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(45) **Date of Patent: Mar. 24, 2015**

(54) **SUBSTITUTED 2-AZA-BICYCLO[2.2.1] HEPTANE-3-CARBOXYLIC ACID (BENZYL-CYANO-METHYL)-AMIDES INHIBITORS OF CATHEPSIN C**

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C07D 498/04	(2006.01)
C07D 487/10	(2006.01)
C07D 405/12	(2006.01)
C07D 209/52	(2006.01)
A61K 31/403	(2006.01)
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A61K 31/4045	(2006.01)
A61K 31/4155	(2006.01)
A61K 31/4192	(2006.01)
A61K 31/438	(2006.01)
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C07D 401/12	(2006.01)
C07D 403/12	(2006.01)
C07D 403/14	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 209/52*** (2013.01); ***A61K 31/403*** (2013.01); ***A61K 31/4035*** (2013.01); ***A61K 31/4045*** (2013.01); ***A61K 31/4155*** (2013.01); ***A61K 31/4192*** (2013.01); ***A61K 31/438*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/5383*** (2013.01); ***A61K 31/551*** (2013.01); ***A61K 45/06*** (2013.01); ***C07D 401/12*** (2013.01); ***C07D 403/12*** (2013.01); ***C07D 403/14*** (2013.01); ***C07D 405/12*** (2013.01); ***C07D 487/10*** (2013.01); ***C07D 498/04*** (2013.01); ***C07D 471/08*** (2013.01)

USPC **514/210.18**; 514/219; 514/249; 514/301; 514/304; 546/125; 540/597; 544/349; 544/362

(58) **Field of Classification Search**

USPC 514/210.18, 219, 249, 301, 304; 546/125; 544/349, 362; 540/597

See application file for complete search history.

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(57) **ABSTRACT**

This invention relates to 2-Aza-bicyclo[2.2.1]heptane-3-carboxylic acid (benzyl-cyano-methyl)-amides of formula 1

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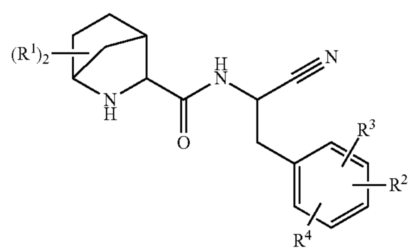

and their use as inhibitors of Cathepsin C, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and/or prevention of diseases connected with dipeptidyl peptidase I activity, e.g. respiratory diseases.

26 Claims, No Drawings

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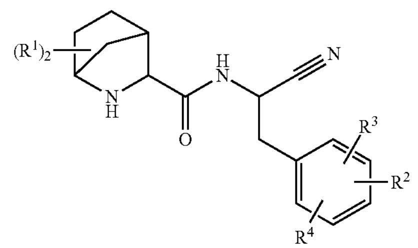
SUBSTITUTED 2-AZA-BICYCLO[2.2.1] HEPTANE-3-CARBOXYLIC ACID (BENZYL-CYANO-METHYL)-AMIDES INHIBITORS OF CATHEPSIN C

FIELD OF INVENTION

This invention relates to substituted 2-Aza-bicyclo[2.2.1] heptane-3-carboxylic acid (benzyl-cyano-methyl)-amides of formula 1



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and their use as inhibitors of Cathepsin C, pharmaceutical compositions containing the same, and methods of using the same as agents for treatment and/or prevention of diseases connected with dipeptidyl peptidase I activity, e.g. respiratory diseases.

BACKGROUND INFORMATION

WO2004110988 discloses peptidyl nitrile inhibitors as dipeptidyl-peptidase I (DPPI) inhibitors for the treatment of a series of diseases.

WO2009074829 and WO2010142985 also disclose peptidyl nitrile inhibitors as dipeptidyl-peptidase I (DPPI) inhibitors for the treatment asthma, COPD or allergic rhinitis.

BRIEF SUMMARY OF THE INVENTION

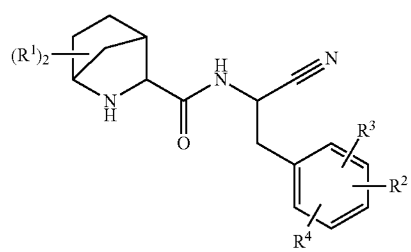
Dipeptidyl-aminopeptidase I (DPPI or Cathepsin C; EC3.4.141), is a lysosomal cysteine protease capable of removing dipeptides from the amino terminus of protein substrates. DPPI was first discovered by Gutman and Fruton in 1948 (J. Biol. Chem. 174: 851-858, 1948). The cDNA of the human enzyme has been described in 1995 (Paris et al.; FEBS Lett 369: 326-330, 1995). The DPPI protein is processed into a mature proteolytically active enzyme consisting of a heavy chain, a light chain, and a propeptide that remains associated with the active enzyme (Wolters et al.; J. Biol. Chem. 273: 15514-15520, 1998). Whereas the other cysteine Cathepsins (e.g. B, H, K, L and S) are monomers, DPPI is a 200-kD tetramer with 4 identical subunits, each composed of the 3 different polypeptide chains. DPPI is constitutively expressed in many tissues with highest levels in lung, kidney, liver and spleen (Kominami et al.; Biol. Chem. Hoppe Seyler 373: 367-373, 1992). Consistent with its role in the activation of serine proteases from hematopoetic cells, DPPI is also relatively highly expressed in neutrophils, cytotoxic lymphocytes, natural killer cells, alveolar macrophages and mast cells. Recent data from DPPI deficient mice suggest that, besides being an important enzyme in lysosomal protein degradation, DPPI also functions as the key enzyme in the activation of granule serine proteases in cytotoxic T lymphocytes and natural killer cells (granzymes A and B; Pham et al.; Proc. Nat. Acad. Sci. 96: 8627-8632, 1999), mast cells (chymase and tryptase; Wolter et al.; J. Biol. Chem. 276: 18551-18556, 2001), and neutrophils (Cathepsin G, elastase and proteinase 3; Adkison et al.; J. Clin. Invest. 109: 363.371, 2002). Once activated, these proteases are capable of degrading various extracellular matrix components, which can lead to tissue damage and chronic inflammation.

Thus, inhibitors of Cathepsin C could potentially be useful therapeutics for the treatment of neutrophil-dominated inflammatory diseases such as chronic obstructive pulmonary disease (COPD), pulmonary emphysema, asthma, multiple sclerosis, and cystic fibrosis (Guay et al.; Curr. Topics Med. Chem. 10: 708-716, 2010; Laine and Busch-Petersen; Expert Opin. Ther. Patents 20: 497-506, 2010). Rheumatoid arthritis is also another chronic inflammatory disease where DPPI appears to play a role. Neutrophils are recruited to the site of joint inflammation and release Cathepsin G, elastase and proteinase 3, proteases which are believed to be responsible for cartilage destruction associated with rheumatoid arthritis. Indeed, DPPI deficient mice were protected against acute arthritis induced by passive transfer of monoclonal antibodies against type II collagen (Adkison et al.; J. Clin. Invest. 109: 363.371, 2002).

In light of the role DPPI plays in activating certain pro-inflammatory serine proteases, it seems desirable to prepare compounds that inhibit its activity, which thereby inhibit downstream serine protease activity. It has been surprisingly found that the bicyclic compounds of the present invention possess potent Cathepsin C activity, high selectivity against other Cathepsins, e.g. Cathepsin K, and in general desirable pharmacokinetic properties.

DETAILED DESCRIPTION OF THE INVENTION

A compound of formula 1



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wherein

R^1 is independently selected from H, C_{1-6}-alkyl-, halogen, HO—, C_{1-6}-alkyl-O—, H_2N—, C_{1-6}-alkyl-HN— and $(C_{1-6}\text{-alkyl})_2N$—, C_{1-6}-alkyl-C(O)HN—;

or two R^1 are together C_{1-4}-alkylene;

R^2 is selected from

$R^{2.1}$;

aryl-; optionally substituted with one, two or three residues independently selected from $R^{2.1}$; optionally substituted with one $R^{2.3}$;

C_{5-10}-heteroaryl-; containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; and

C_{5-10}-heterocyclyl-; containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three or four $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$ or

R^2 and R^4 are together with two adjacent carbon atoms of the phenyl ring a 5- or 6-membered aryl or heteroaryl, containing one, two or three heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$;

$R^{2.1}$ is independently selected from among H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-6}-alkylene-, $R^{2.1.1}$-A-, C_{1-6}-alkyl-A-, C_{3-8}-cycloalkyl-A-, C_{1-6}-haloalkyl-A-, $R^{2.1.1}$—C_{1-6}-alkylene-A-, C_{1-6}-alkyl-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-A-C_{1-6}-alkylene-, C_{1-6}-haloalkyl-A-C_{1-6}-alkylene-, $R^{2.1.1}$—C_{1-6}-alkylene-A-C_{1-6}-alkylene-, $R^{2.1.1}$-A-C_{1-6}-alkylene-, HO—C_{1-6}-alkylene-A-, HO—C_{1-6}-alkylene-A-C_{1-6}-alkylene-, C_{1-6}-alkyl-O—C_{1-6}-alkylene-A- and C_{1-6}-alkyl-O—C_{1-6}-alkylene-A-C_{1-6}-alkylene-;

$R^{2.1.1}$ is independently selected from

aryl-; optionally substituted independently from each other with one, two or three $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-; containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

C_{5-10}-heterocyclyl-; containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three or four $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

$R^{2.1.1.1}$ is independently selected from among halogen, HO—, O═, C_{1-6}-alkyl-, C_{1-6}-alkyl-O—, C_{1-6}-haloalkyl-, C_{1-6}-haloalkyl-O— and C_{3-8}-cycloalkyl-;

$R^{2.1.1.2}$ is independently selected from among O═, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-O—C_{1-6}-alkyl-, H(O)C—, C_{1-6}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl-;

$R^{2.2}$ is independently selected from among H-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-A-C_{1-6}-alkylene-, C_{1-6}-haloalkyl-A-C_{1-6}-alkylene-, $R^{2.1.1}$-A-C_{1-6}-alkylene-, C_{1-6}-alkyl-S$(O)_2$—, C_{1-6}-alkyl-C(O)— and $R^{2.1.1}$-A-;

$R^{2.3}$ and R^4 are together selected from among —O—, —S—, —N($R^{2.3.1}$)—, —C(O)N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C(O)—, —$S(O)_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, —$S(O)_2$—, $R^{2.3}$, $R^{2.3}$, —C($R^{2.3.2}$)═C($R^{2.3.2}$)—, —C═N—, —N═C—, —C$(R^{2.3.2})_2$—O—, —O—C$(R^{2.3.2})_2$—, —C$(R^{2.3.2})_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C$(R^{2.3.2})_2$— and —C_{1-4}-alkylene-;

$R^{2.3.1}$ is independently selected from among H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and, $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-;

$R^{2.3.2}$ is independently selected from among H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-;

$R^{2.4}$ and R^4 are together selected from among —N($R^{2.4.1}$)—, —C(O)N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C(O)—, —$S(O)_2$N($R^{2.4.1}$)—, —N($R^{2.4.1}$)$S(O)_2$—, —C(O)—, —S(O)—, —$S(O)_2$—, —C($R^{2.4.2}$)═C($R^{2.4.2}$)—, —C═N—, —N═C—, —C$(R^{2.4.2})_2$N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C$(R^{2.4.2})_2$— and —C_{1-4}-alkylene-; and

$R^{2.4.1}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene-, $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-;

$R^{2.4.2}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-;

$R^{2.5}$ and R^4 are together selected from —C($R^{2.5.1}$)═, ═C($R^{2.5.1}$)— and —N═; and

$R^{2.5.1}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-;

R^3 is H or F;

R^4 is independently selected from F, Cl, phenyl-H_2C—O—, HO—, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-, C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-O—, C_{1-6}-haloalkyl-O—, C_{1-6}-alkyl-HN—, $(C_{1-6}\text{-alkyl})_2$-HN—, C_{1-6}-alkyl-HN—C_{1-4}-alkylene- and $(C_{1-6}\text{-alkyl})_2$-HN—C_{1-4}-alkylene-;

A is a bond or independently selected from —O—, —S—, —N(R^5)—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —S(O)(═NR^5)—N(R^5)—, —N(R^5)(NR^5═)S(O)—, —S$(═NR^5)_2$—N(R^5)—, —N(R^5)$(NR^5═)_2$S—, —C(R^5)═C(R^5)—, —C≡C—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, —$S(O)_2$—, —S(═NR^5)—, —S(O)(═NR^5)—, —S$(═NR^5)_2$—, —(R^5)(O)S═N—, —(R^5N═)(O)S— and —N═(O)(R^5)S—;

R^5 is independently selected from H, C_{1-6}-alkyl- and NC—; or a salt thereof.

PREFERRED EMBODIMENTS

Preferred are the above compounds of formula 1, wherein R^1 is $R^{1.a}$ and $R^{1.a}$ is independently selected from H, C_{1-4}-alkyl-, F and HO—.

Preferred are the above compounds of formula 1, wherein R^1 is $R^{1.b}$ and $R^{1.b}$ is H.

Preferred are the above compounds of formula 1, wherein R^1 is $R^{1.c}$ and two $R^{1.c}$ are together —CH_2—.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.a}$ and $R^{2.a}$ is $R^{2.1}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.b}$ and $R^{2.b}$ is $R^{2.1.a}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.c}$ and $R^{2.c}$ is aryl-; optionally substituted with one, two or three residues independently selected from $R^{2.1}$; optionally substituted with one $R^{2.3}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.d}$ and $R^{2.d}$ is phenyl; optionally substituted with one, two or three residues independently selected from $R^{2.1}$; optionally substituted with one $R^{2.3}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.d}$ and $R^{2.d}$ is phenyl; optionally substituted with one, two or three residues independently selected from $R^{2.1}$ and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

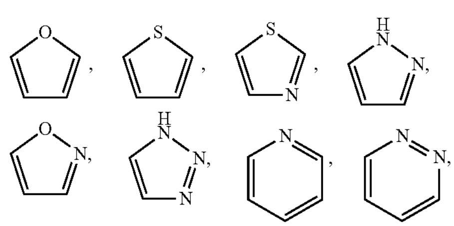
C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.g}$ and $R^{2.g}$ is selected from



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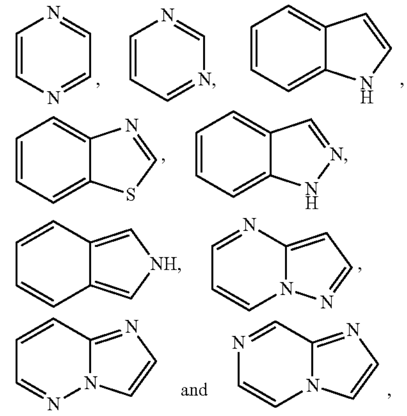


wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

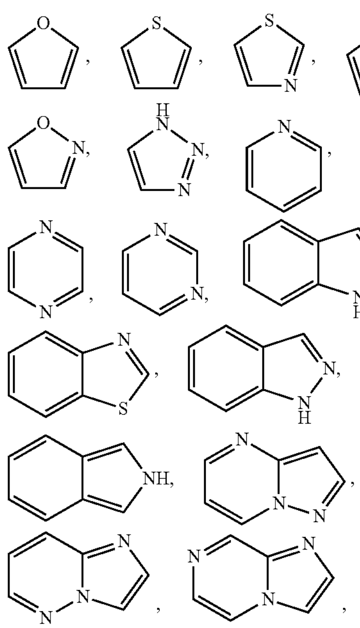
$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-S$(O)_2$— and C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.e}$ and $R^{2.e}$ is $C_{5\ or\ 6}$-heteroaryl-, containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.f}$ and $R^{2.f}$ is bicyclic C_{7-10}-heteroaryl-, each containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.g}$ and $R^{2.g}$ is selected from

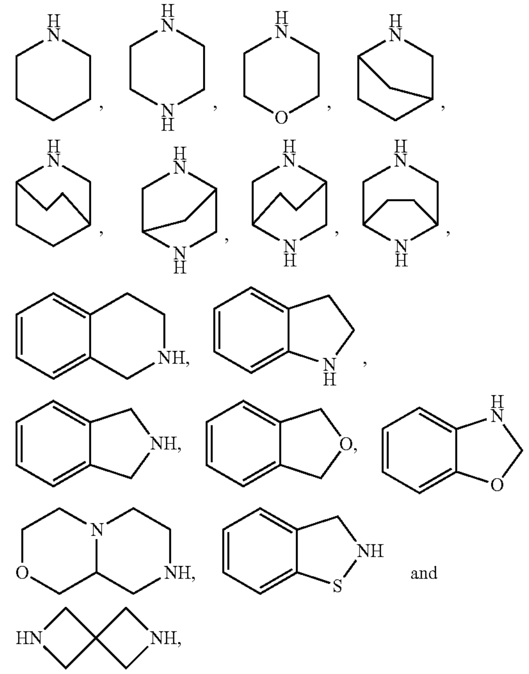


wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.h}$ and $R^{2.h}$ is selected from pyrazole, thiophene and furane, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

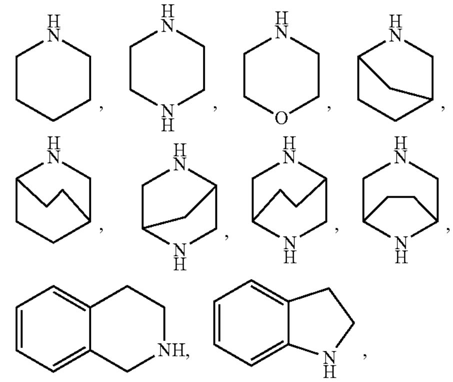
Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.i}$ and $R^{2.i}$ is selected from C_6-heterocyclyl- and C_{7-10}-heterocyclyl-, each containing one, two, three or four heteroatoms independently selected from S, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.j}$ and $R^{2.j}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.j}$ and $R^{2.j}$ is selected from



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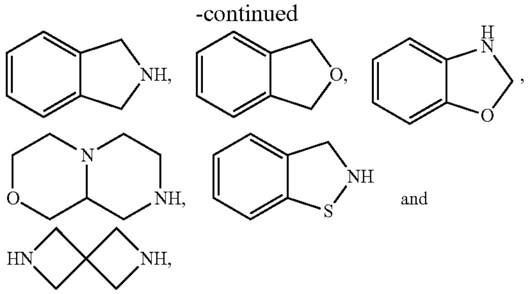


wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

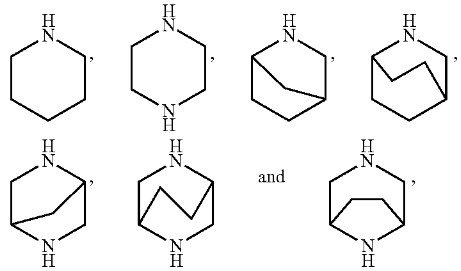
C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl; and

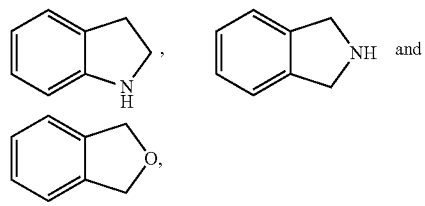
$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-S$(O)_2$— and C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.k}$ and $R^{2.k}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$

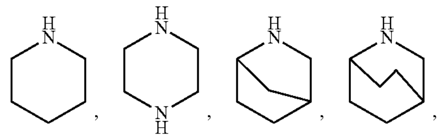
Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.l}$ and $R^{2.l}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.m}$ and $R^{2.m}$ is together with R^4 and two adjacent carbon atoms of the phenyl ring a 5- or 6-membered aryl or heteroaryl, containing one, two or three heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, preferably pyrazole, naphtene, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.n}$ and $R^{2.n}$ is selected from aryl-, pyrazole, thiophene and furane; wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; or $R^{2.n}$ is selected from



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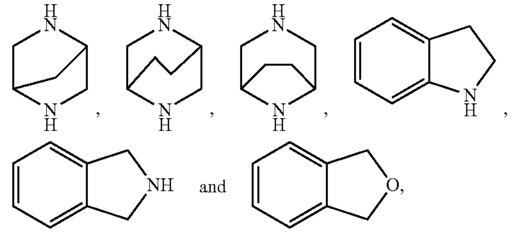
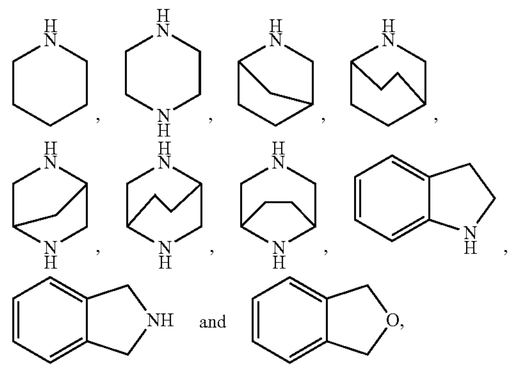


wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.o}$ and $R^{2.o}$ is selected from aryl-, pyrazole, thiophene and furane; wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

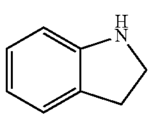
Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.p}$ and $R^{2.p}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.q}$ and $R^{2.q}$ is selected from among the substituents (a1) to (q1)

(a1)



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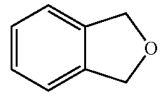
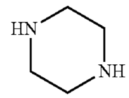
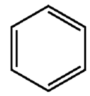
(b1)



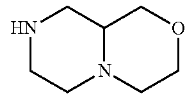
(c1)



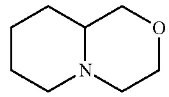
(d1)



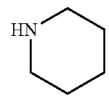
(e1)



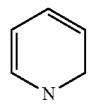
(f1)



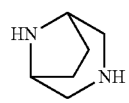
(g1)



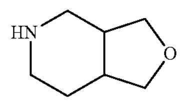
(h1)



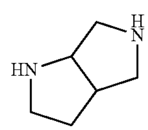
(i1)



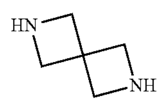
(j1)



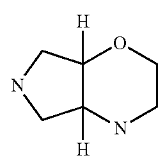
(k1)



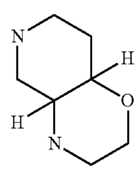
(l1)



(m1)



(n1)



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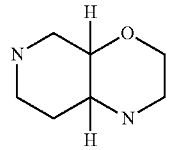
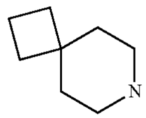
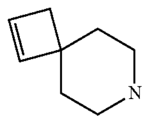
(o1)



(p1)



(q1)



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other are substituted with $R^{2.2}$;

Particularly preferred $R^{2.q}$ is substituent (a1) or (c1), wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other are substituted with $R^{2.2}$

Particularly preferred $R^{2.q}$ denotes a substituent selected from the group (a1) to (q1), wherein carbon atoms of the ring are optionally and independently from each other substituted with a group selected from among =O, Me, $MeSO_2$—, Me-piperazinyl-SO_2—, morpholinyl, —CN and F, and possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with Me_2N—CH_2—CH_2—, F_2CH—CH_2—, —CH_3 and tetrahydrofuranyl.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.s}$ and $R^{2.s}$ is Phenyl-$R^{2.3}$, wherein the phenyl ring is optionally substituted with one or two residues $R^{2.1}$, wherein

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O=, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

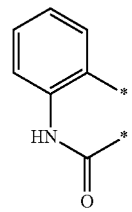
C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O=, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.2}$ is independently selected from O=, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

and $R^{2.s}$ and R^4 together denote a group (r1),

(r1)

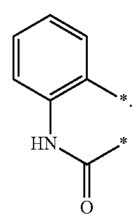


wherein the N-atom is optionally substituted with —$R^{2.2}$, wherein

$R^{2.2}$ is independently selected from H-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-A-C_{1-6}-alkylene-, C_{1-6}-haloalkyl-A-C_{1-6}-alkylene-, $R^{2.1.1}$-A-C_{1-6}-alkylene-, C_{1-6}-alkyl-$S(O)_2$—, C_{1-6}-alkyl-C(O)— and $R^{2.1.1}$-A-.

Particularly preferred are the above compounds of formula 1, wherein R^2 is $R^{2.s}$ and $R^{2.s}$ is Phenyl-$R^{2.3}$, wherein the phenyl ring is optionally substituted with one or two residues independently selected from F and —CN, and $R^{2.s}$ and R^4 together denote a group (r1), wherein the N-atom is optionally substituted with —CH_3,

(r1)



Particularly preferred are the above compounds of formula 1, wherein

R^1 is H,

R^3 is H or F, preferably F,

and

R^2 is $R^{2.s}$ and $R^{2.s}$ is Phenyl-$R^{2.3}$,

wherein the phenyl ring is optionally substituted with one or two residues independently selected from F and —CN,

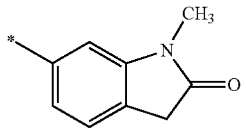
and $R^{2.s}$ and R^4 together denote a group (r1), wherein the N-atom is optionally substituted with —CH_3;

Particularly preferred are the above compounds of formula 1, wherein $R^{2.s}$ and R^4 together denote a group (r1), optionally substituted as described above, in meta and para position of the phenyl ring.

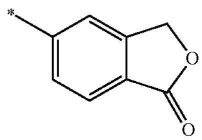
Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.r}$ and $R^{2.r}$ is selected from among the substituents (a2) to (w2) or

R^2 together with R^4 denotes a group selected from among (a3) to (e3).

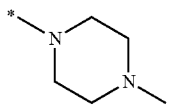
(a2)



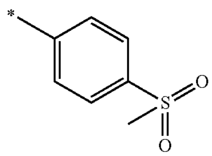
(b2)



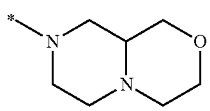
(c2)



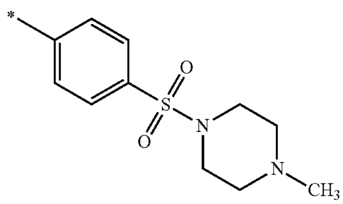
(d2)



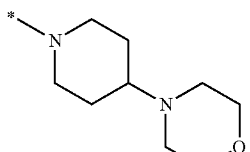
(e2)



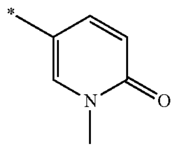
(f2)



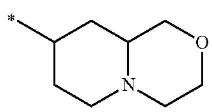
(g2)



(h2)



(i2)



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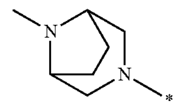
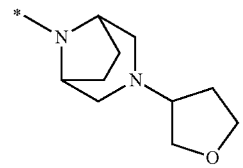
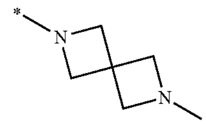
(2j)



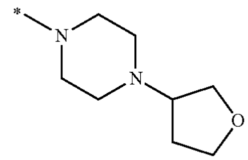
(k2)



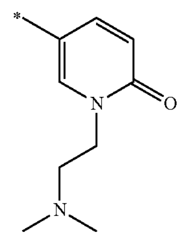
(l2)



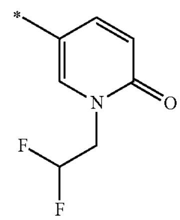
(m2)



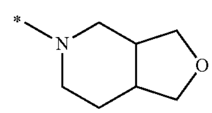
(n2)



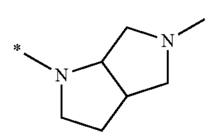
(o2)



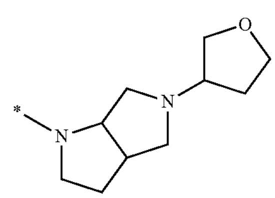
(p2)



(q2)



(r2)



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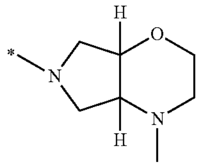
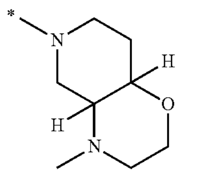
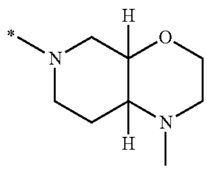
(s2)



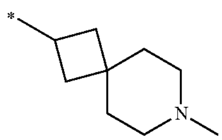
(t2)



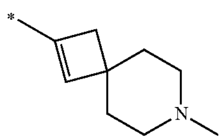
(u2)



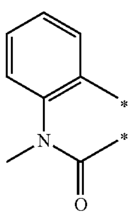
(v2)



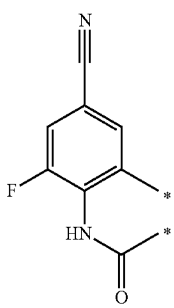
(w2)



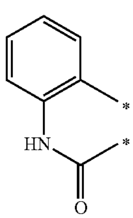
(a3)



(b3)



(c3)



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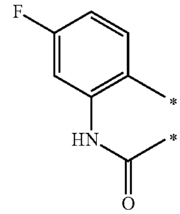
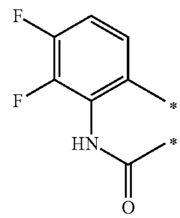
(d3)



(e3)



Particularly preferred $R^{2.r}$ is substituent (a2) or (c2).

Particularly preferred R^2 is substituted Phenyl-$R^{2.3}$ wherein R^2 together with R^4 denotes a group selected from among (a3), (b3), (c3), (d3) and (e3).

Preferred are the above compounds of formula 1, wherein $R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O=, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-.

Preferred are the above compounds of formula 1, wherein $R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$

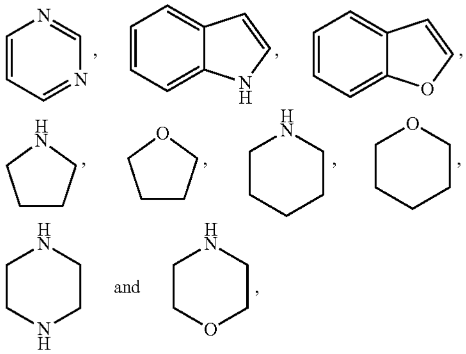
and

C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other are substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O=, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O=, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

Preferred are the above compounds of formula 1, wherein $R^{2.1.1}$ is $R^{2.1.1.b}$ and $R^{2.1.1.b}$ is phenyl or selected from

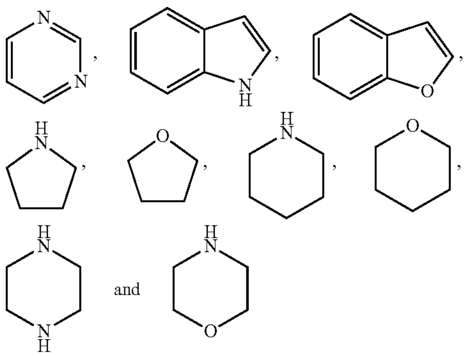


wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

Preferred are the above compounds of formula 1, wherein $R^{2.1.1}$ is $R^{2.1.1.c}$ and $R^{2.1.1.c}$ is phenyl or selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from F, Cl, Me, MeO— and cyclopropyl-; and

$R^{2.1.1.2}$ is independently selected from Me, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

Preferred are the above compounds of formula 1, wherein $R^{2.1.2}$ is $R^{2.1.2.a}$ and $R^{2.1.2.a}$ is selected from H, NC—, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene- and (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-.

Preferred are the above compounds of formula 1, wherein $R^{2.1.2}$ is $R^{2.1.2.b}$ and $R^{2.1.2.b}$ is selected from H, C_{1-4}-alkyl-, and C_{3-6}-cycloalkyl-;

Preferred are the above compounds of formula 1, wherein $R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-S(O)$_2$— and C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-;

Preferred are the above compounds of formula 1, wherein $R^{2.2}$ is $R^{2.2.b}$ and $R^{2.2.b}$ is together with R^4 selected from —C(O)—, —S(O)—, —S(O)$_2$—, —C($R^{2.1.2}$)═C($R^{2.1.2}$)— and —C_{1-4}-alkylene-;

Preferred are the above compounds of formula 1, wherein $R^{2.3}$ is together with R^4 a group $R^{2.3.a}$ and $R^{2.3.a}$ is selected from —O—, —S—, —N($R^{2.3.1}$)—, —C(O)N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C(O)—, —S(O)$_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)S(O)$_2$—, —C(O) O—, —OC(O)—, —C(O)—, —S(O)—, —S(O)$_2$—, —C($R^{2.3.2}$)═C($R^{2.3.2}$)—, —C═N—, —N═C—, —C($R^{2.3.2}$)$_2$—O—, —O—C($R^{2.3.2}$)$_2$—, —C($R^{2.3.2}$)$_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C($R^{2.3.2}$)$_2$— and —C_{1-4}-alkylene-; and

$R^{2.3.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and (C_{1-4}-alkyl)$_2$N—C_{1-4}-alkylene-;

$R^{2.3.2}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and (C_{1-4}-alkyl)$_2$N—C_{1-4}-alkylene-.

Preferred are the above compounds of formula 1, wherein $R^{2.4}$ is together with R^4 a group $R^{2.4.a}$ and $R^{2.4.a}$ is selected from —N($R^{2.4.1}$)—, —C(O)N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C(O)—, —S(O)$_2$N($R^{2.4.1}$)—, —N($R^{2.4.1}$)S(O)$_2$—, —C(O)—, —S(O)—, —S(O)$_2$—, —C($R^{2.4.2}$)═C($R^{2.4.2}$)—, —C═N—, —N═C—, —C($R^{2.4.2}$)$_2$N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C($R^{2.4.2}$)$_2$— and —C_{1-4}-alkylene-; and

$R^{2.4.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and (C_{1-4}-alkyl)$_2$N—C_{1-4}-alkylene-;

$R^{2.4.2}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene-, (C_{1-4}-alkyl)$_2$N—C_{1-4}-alkylene-.

Preferred are the above compounds of formula 1, wherein $R^{2.5}$ is together with R^4 a group $R^{2.5.a}$ and $R^{2.5.a}$ is selected from —C($R^{2.5.1}$)═, ═C($R^{2.5.1}$)— and —N═; and

$R^{2.5.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and (C_{1-4}-alkyl)$_2$N—C_{1-4}-alkylene-.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.m}$ and $R^{2.m}$ is together with R^4 and two adjacent carbon atoms of the phenyl ring a 5- or 6-membered aryl or heteroaryl, containing one, two or three heteroatoms independently selected from S, S(O), S(O)$_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-

alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

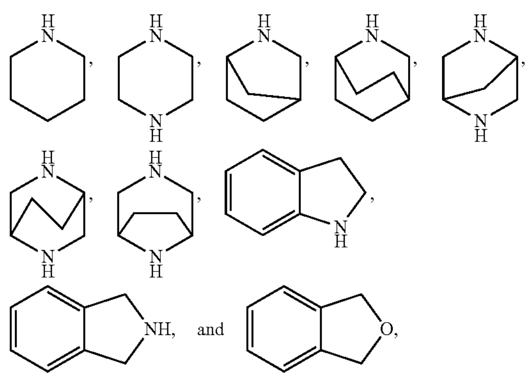
C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$ and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-S$(O)_2$— and C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-.

Preferred are the above compounds of formula 1, wherein R^2 is $R^{2.n}$ and $R^{2.n}$ is selected from aryl-, pyrazole, thiophene and furane; wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; or $R^{2.n}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-S$(O)_2$— and C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-; and

$R^{2.3}$ is together with R^4 a group $R^{2.3.a}$ and $R^{2.3.a}$ is selected from —O—, —S—, —N($R^{2.3.1}$)—, —C(O)N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C(O)—, —$S(O)_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, —$S(O)_2$—, —C($R^{2.3.2}$)═C($R^{2.3.2}$)—, —C═N—, —N═C—, —C$(R^{2.3.2})_2$—O—, —O—C$(R^{2.3.2})_2$—, —C$(R^{2.3.2})_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C$(R^{2.3.2})_2$— and —C_{1-4}-alkylene-; and

$R^{2.3.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

$R^{2.3.2}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-; and

$R^{2.4}$ is together with R^4 a group $R^{2.4.a}$ and $R^{2.4.a}$ is selected from —N($R^{2.4.1}$)—, —C(O)N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C

(O)—, —$S(O)_2N(R^{2.4.1})$—, —$N(R^{2.4.1})S(O)_2$—, —C(O)—, —S(O)—, —$S(O)_2$—, —$C(R^{2.4.2})$=$C(R^{2.4.2})$—, —C=N—, —N=C—, —$C(R^{2.4.2})_2N(R^{2.4.1})$—, —$N(R^{2.4.1})C(R^{2.4.2})_2$— and —$C_{1-4}$-alkylene-; and

$R^{2.4.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-;

$R^{2.4.2}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-; and

$R^{2.5}$ is together with R^4 a group $R^{2.5.a}$ and $R^{2.5.a}$ is selected from —$C(R^{2.5.1})$=, =$C(R^{2.5.1})$— and —N=; and

$R^{2.5.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2N$—$C_{1-4}$-alkylene-.

Preferred are the above compounds of formula 1, wherein R^1 is $R^{1.b}$ and $R^{1.b}$ is H; or two R^1 are together —CH_2—;

R^2 is selected from

$R^{2.1}$;

phenyl-; optionally substituted with one or two residues independently selected from $R^{2.1}$; optionally substituted with one $R^{2.3}$;

C_5-heteroaryl-; containing two or three independently selected from S, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one $R^{2.2}$;

monocyclic C_6-heterocyclyl containing one or two nitrogen atoms, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one $R^{2.2}$; and

bicyclic $C_{9\ or\ 10}$-heterocyclyl-; containing one, two, three or four heteroatoms independently selected from $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one $R^{2.2}$;

$R^{2.1}$ is independently selected from halogen, NC—, O=, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, $R^{2.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, and HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-;

$R^{2.1.1}$ is independently selected from

phenyl-; and

$C_{5\ or\ 6}$-heterocyclyl-; containing one or two heteroatoms independently selected from O and N, wherein the ring is fully or partially saturated, wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one C_{1-4}-alkyl-;

$R^{2.2}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene- and C_{1-4}-alkyl-C(O)—;

$R^{2.3}$ and R^4 are together a group selected from —$N(R^{2.3.1})$—, —$C(O)N(R^{2.3.2})$— and —$N(R^{2.3.1})C(O)$—;

$R^{2.3.1}$ is independently selected from H and H_3C—;

R^3 is H or F;

R^4 is $R^{4.b}$ and $R^{4.b}$ is F;

A is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2N(R^5)$—, —$N(R^5)S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —$S(O)_2$— and —N=(O)(R^5)S—;

R^5 is independently selected from H and C_{1-4}-alkyl-;

or a salt thereof.

Preferred are the above compounds of formula 1, wherein R^2 is selected from the Table $1R^2$—Embodiments of the invention for R^2, $R^{2.1}$, $R^{2.1.1}$, $R^{2.2}$, $R^{2.3}$, $R^{2.4}$ and $R^{2.5}$ (if present):

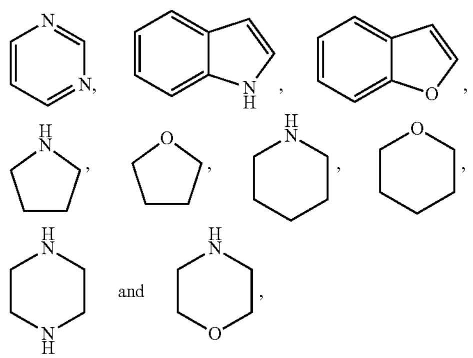
E#	R^2	$R^{2.1}$	$R^{2.1.1}$	$R^{2.2}$	$R^{2.3-5}$
1	$R^{2.a}$	$R^{2.1}$	$R^{2.1.1.a}$		—
2	$R^{2.a}$	$R^{2.1}$	$R^{2.1.1.b}$		—
3	$R^{2.a}$	$R^{2.1}$	$R^{2.1.1.c}$		—
4	$R^{2.b}$	$R^{2.1.a}$	$R^{2.1.1.a}$		—
5	$R^{2.b}$	$R^{2.1.a}$	$R^{2.1.1.b}$		—
6	$R^{2.b}$	$R^{2.1.a}$	$R^{2.1.1.c}$		—
7	$R^{2.c}$	$R^{2.1.a}$	$R^{2.1.1.a}$	—	—
8	$R^{2.c}$	$R^{2.1.a}$	$R^{2.1.1.b}$	—	—
9	$R^{2.c}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	—
10	$R^{2.c}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.3.a}$
11	$R^{2.c}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.4.a}$
12	$R^{2.c}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.5.a}$
13	$R^{2.d}$	$R^{2.1.a}$	$R^{2.1.1.a}$	—	—
14	$R^{2.d}$	$R^{2.1.a}$	$R^{2.1.1.b}$	—	—
15	$R^{2.d}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	—
16	$R^{2.d}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.3.a}$
17	$R^{2.d}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.4.a}$
18	$R^{2.d}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.5.a}$
19	$R^{2.e}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
20	$R^{2.e}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
21	$R^{2.e}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
22	$R^{2.f}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
23	$R^{2.f}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
24	$R^{2.f}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
25	$R^{2.g}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
26	$R^{2.g}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
27	$R^{2.g}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
28	$R^{2.h}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
29	$R^{2.h}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
30	$R^{2.h}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
31	$R^{2.e}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.3.a}$
32	$R^{2.e}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.4.a}$
33	$R^{2.e}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.5.a}$
34	$R^{2.g}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.3.a}$
35	$R^{2.g}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.4.a}$
36	$R^{2.g}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.5.a}$
37	$R^{2.h}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.3.a}$
38	$R^{2.h}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.4.a}$
39	$R^{2.h}$	$R^{2.1.a}$	$R^{2.1.1.c}$	—	$R^{2.5.a}$
40	$R^{2.i}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
41	$R^{2.i}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
42	$R^{2.i}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
43	$R^{2.j}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
44	$R^{2.j}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
45	$R^{2.j}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
46	$R^{2.k}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
47	$R^{2.k}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
48	$R^{2.k}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—
49	$R^{2.l}$	$R^{2.1.a}$	$R^{2.1.1.a}$	$R^{2.2.a}$	—
50	$R^{2.l}$	$R^{2.1.a}$	$R^{2.1.1.b}$	$R^{2.2.a}$	—
51	$R^{2.l}$	$R^{2.1.a}$	$R^{2.1.1.c}$	$R^{2.2.a}$	—

For a better understanding of the Table $1R^2$—Embodiments of the invention example (E#) 21, can also be read as a group R^2, wherein

R^2 is $R^{2.e}$ and $R^{2.e}$ is $C_{5\ or\ 6}$-heteroaryl-, containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O=, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.c}$ and $R^{2.1.1.c}$ is phenyl or selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$ wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from F, Cl, Me, MeO— and cyclopropyl-; and

$R^{2.1.1.2}$ is independently selected from Me, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-$S(O)_2$—, C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-.

Preferred are the above compounds of formula 1, wherein R^3 is $R^{3.a}$ and $R^{3.a}$ is H.

Preferred are the above compounds of formula 1, wherein R^3 is $R^{3.b}$ and $R^{3.b}$ is F.

Preferred are the above compounds of formula 1, wherein R^4 is $R^{4.a}$ and $R^{4.a}$ is selected from F, Cl, phenyl-H_2C—O—, HO—, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O— and C_{1-4}-haloalkyl-O—.

Preferred are the above compounds of formula 1, wherein R^4 is $R^{4.b}$ and $R^{4.b}$ is F; preferably in ortho position.

Preferred are the above compounds of formula 1, wherein A is A^a and A^a is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —$S(O)_2$—, —(R^5)(O)S=N—, —(R^5N=)(O)S— and —N=(O)(R^5)S— and R^5 is $R^{5.a}$ and $R^{5.a}$ is independently selected from H, C_{1-4}-alkyl- and NC—.

Preferred is a compound of formula 1, wherein

R^1 is independently selected from H, C_{1-4}-alkyl-, halogen, HO—, C_{1-4}-alkyl-O—, H_2N—, C_{1-6}-alkyl-HN—, (C_{1-6}-alkyl)$_2$N— and C_{1-6}-alkyl-C(O)HN—;

or two R^1 are together C_{1-4}-alkylene;

R^2 is selected of the examples of the Table 1R^2—Embodiments of the invention; preferably examples (E#) 7-51, preferably one of the groups selected from 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40, 41, 42, 43, 44, 45, 45, 46, 47, 48, 49, 50, 51;

R^3 is H or F;

R^4 is independently selected from F, Cl, phenyl-H_2C—O—, HO—, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-, C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-O—, C_{1-6}-haloalkyl-O—, C_{1-6}-alkyl-HN—, (C_{1-6}-alkyl)$_2$-HN—, C_{1-6}-alkyl-HN—C_{1-4}-alkylene- and (C_{1-6}-alkyl)$_2$-HN—C_{1-4}-alkylene-;

A is a bond or independently selected from —O—, —S—, —N(R^5)—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —S(O)(=NR^5)—N(R^5)—, —N(R^5)(NR^5=), S(O)—, —S(=NR^5)$_2$—N(R^5)—, —N(R^5)(NR^5=)$_2$S—, —C(R^5)=C(R^5)—, —C≡C—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, $S(O)_2$—, —S(=NR^5)—, —S(O)(=NR^5)—, —S(=NR^5)$_2$—, —(R^5)(O)S=N—, —(R^5N=)(O)S— and —N=(O)(R^5)S—;

R^5 is independently selected from H, C_{1-6}-alkyl- and NC—;

or a salt thereof.

Preferred is a compound of formula 1, wherein

R^1 is $R^{1.a}$ and $R^{1.a}$ is independently selected from H, C_{1-4}-alkyl-, F and HO—.

or two R^1 are together C_{1-4}-alkylene;

R^2 is selected of the examples of the Table 1R^2—Embodiments of the invention; preferably examples (E#) 7-51, preferably one of the groups selected from 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40, 41, 42, 43, 44, 45, 45, 46, 47, 48, 49, 50, 51;

R^3 is H or F;

R^4 is $R^{4.a}$ and $R^{4.a}$ is F, Cl, phenyl-H_2C—O—, HO—, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O— and C_{1-4}-haloalkyl-O—;

A is a bond or independently selected from —O—, —S—, —N(R^5)—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —S(O)(=NR^5)—N(R^5)—, —N(R^5)(NR^5=)S(O)—, —S(=NR^5)$_z$—N(R^5)—, —N(R^5)(NR^5=)$_2$S—, —C(R^5)=C(R^5)—, —C≡C—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, $S(O)_2$—, —S(=NR^5)—, —S(O)(=NR^5)—, —S(=NR^5)$_2$—, —(R^5)(O)S=N—, —(R^5N=)(O)S— and —N=(O)(R^5)S—;

R^5 is independently selected from H, C_{1-6}-alkyl- and NC—;

or a salt thereof.

Preferred is a compound of formula 1, wherein

R^1 is $R^{1.a}$ and $R^{1.a}$ is independently selected from H, C_{1-4}-alkyl-, F and HO—.

or two R^1 are together C_{1-4}-alkylene;

R^2 is selected of the examples of the Table 1R^2—Embodiments of the invention; preferably examples (E#) 7-51, preferably one of the groups selected from 13, 14, 15, 16, 17, 18 or 25, 26, 27, 28, 29, 30, 34, 35, 36, 37, 38, 39 or 43, 44, 45, 46, 47 and 48;

R^3 is H or F;

R^4 is $R^{4.a}$ and $R^{4.a}$ is selected from F, Cl, phenyl-H_2C—O—, HO—, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O— and C_{1-4}-haloalkyl-O—;

A is A^a and A^a is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, $S(O)_2$—, —(R^5)(O)S═N—, —(R^5N═)(O)S— and —N═(O)(R^5)S—;

R^5 is $R^{5.a}$ and $R^{5.a}$ is independently selected from H, C_{1-4}-alkyl- and NC—;

or a salt thereof.

Preferred is a compound of formula 1, wherein

R^1 is $R^{1.b}$ and $R^{1.b}$ is H; or two R^1 are together —CH_2—;

R^2 is selected of the examples of the Table 1R^2—Embodiments of the invention; preferably examples (E#) 7-51, preferably one of the groups selected from 13, 14, 15, 16, 17, 18 or 25, 26, 27, 28, 29, 30, 34, 35, 36, 37, 38, 39 or 43, 44, 45, 46, 47 and 48;

R^3 is H or F;

R^4 is $R^{4.b}$ and $R^{4.b}$ is F;

A is A^a and A^a is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, $S(O)_2$—, —(R^5)(O)S═N—, —(R^5N═)(O)S— and —N═(O)(R^5)S—;

R^5 is $R^{5.a}$ and $R^{5.a}$ is independently selected from H, C_{1-4}-alkyl- and NC—;

or a salt thereof.

Preferred is a compound of formula 1, wherein

R^1 is $R^{1.b}$ and $R^{1.b}$ is H; or two R^1 are together —CH_2—;

R^2 is selected of the examples of the Table 1R^2—Embodiments of the invention; preferably examples (E#) 7-51, preferably one of the groups selected from 13, 14, 15, 16, 17, 18 or 25, 26, 27, 28, 29, 30, 34, 35, 36, 37, 38, 39 or 43, 44, 45, 46, 47 and 48;

R^3 is H or F;

R^4 is $R^{4.b}$ and $R^{4.b}$ is F;

A is A^a and A^a is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, $S(O)_2$—, —(R^5)(O)S═N—, —(R^5N═)(O)S— and —N═(O)(R^5)S—;

R^5 is $R^{5.a}$ and $R^{5.a}$ is independently selected from H, C_{1-4}-alkyl- and NC—;

or a salt thereof.

Preferred is a compound of formula 1, wherein

R^1 is $R^{1.b}$ and $R^{1.b}$ is H; or two R^1 are together —CH_2—;

R^2 is selected from

$R^{2.1}$;

phenyl-; optionally substituted with one or two residues independently selected from $R^{2.1}$; optionally substituted with one $R^{2.3}$;

C_5-heteroaryl-; containing two or three independently selected from S, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one $R^{2.2}$;

monocyclic C_6-heterocyclyl containing one or two nitrogen atoms, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one $R^{2.2}$; and

bicyclic $C_{9\ or\ 10}$-heterocyclyl-; containing one, two, three or four heteroatoms independently selected from $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one $R^{2.2}$;

$R^{2.1}$ is independently selected from halogen, NC—, O═, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; preferably F, NC—, O═, H-A-, H-A-CH_2—, $R^{2.1.1}$-A-, H_3C-A-, H_3C—CH_2-A-, Cyclopropyl-A-, $R^{2.1.1}$—CH_2—CH_2-A-, $R^{2.1.1}$—CH_2-A-, H_3C-A-CH_2—CH_2— and HO—C_4-alkylene-A-CH_2—;

$R^{2.1.1}$ is independently selected from

phenyl-; and

$C_{5\ or\ 6}$-heterocyclyl-; containing one or two heteroatoms independently selected from O and N, wherein the ring is fully or partially saturated, wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one C_{1-4}-alkyl-; preferably H_3C—;

$R^{2.2}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-C(O)—; preferably H-A-CH_2—, H-A-CH_2—CH_2—, cyclopropyl-, H_3C-A-CH_2—CH_2—, $R^{2.1.1}$-A-CH_2— and H_3C—C(O)—;

$R^{2.3}$ and R^4 are together a group selected from —N($R^{2.3.1}$)—, —C(O)N($R^{2.3.2}$)— or —N($R^{2.3.1}$)C(O)—;

$R^{2.3.1}$ is independently selected from H and H_3C—;

R^3 is H or F;

R^4 is $R^{4.b}$ and $R^{4.b}$ is F;

A is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —$S(O)_2$— and —N═(O)(R^5)S—;

R^5 is independently selected from H or C_{1-4}-alkyl-;

or a salt thereof.

Preferred are the above compounds of formula 1, wherein

R^3 is $R^{3.a}$ and $R^{3.a}$ is H, and

R^4 is $R^{4.b}$ and $R^{4.b}$ is F;

Particularly preferred are the above compounds of formula 1, wherein

R^3 is H,

R^4 is F and

R^2 is $R^{2.q}$ and $R^{2.q}$ is selected from among the substituents (a1) to (q1).

Particularly preferred are the above compounds of formula 1, wherein

R^3 is F and

R^2 and R^4 together denote a group selected from among (r1) to (t1).

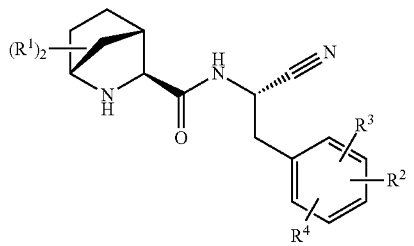
Preferably (a1) to (q1) or (r1) to (t1) are independently substituted by a substituent selected from among

═O, Me, $MeSO_2$—, Me-piperazinyl-SO_2—, morpholinyl, furanyl, Me_2N—CH_2—CH_2—, F_2CH—CH_2—, —CN and F.

Preferred are the compounds of formula I, wherein the compounds are selected from the group consisting of examples 2, 3, 6, 16, 43, 155, 193, 249, 250, 254, 283, 284, 322, 323, 324, 325, 326, 328, 329, 330, 331, 333, 342, 343, 351, 352, 353, 354, 355, 356, 357, 358 and 359.

Particularly preferred are the compounds of formula I, wherein the compounds are selected from the group consisting of examples 322, 323, 324, 325 and 326.

Preferred are the above compounds of formula 1, in its enantiomerically pure form of formula 1'



1'

wherein R^1, R^2, R^3 and R^4 have the above mentioned meaning.

USED TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms.

In general in single groups like HO, H_2N, S(O), $S(O)_2$, NC (cyano), HOOC, F_3C or the like, the skilled artisan can see the radical attachment point(s) to the molecule from the free valences of the group itself. For combined groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C_{1-4}-alkyl-" means an aryl group which is bound to a C_{1-4}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

Alternatively "*" indicates within a chemical entity the binding site, i.e. the point of attachment.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk is may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Many of the followings terms may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound.

The expressions "prevention", "prophylaxis", "prophylactic treatment" or "preventive treatment" used herein should be understood synonymous and in the sense that the risk to develop a condition mentioned hereinbefore is reduced, especially in a patient having elevated risk for said conditions or a corresponding anamnesis, e.g. elevated risk of developing metabolic disorder such as diabetes or obesity or another disorder mentioned herein. Thus the expression "prevention of a disease" as used herein means the management and care of an individual at risk of developing the disease prior to the clinical onset of the disease. The purpose of prevention is to combat the development of the disease, condition or disorder, and includes the administration of the active compounds to prevent or delay the onset of the symptoms or complications and to prevent or delay the development of related diseases, conditions or disorders. Success of said preventive treatment is reflected statistically by reduced incidence of said condition within a patient population at risk for this condition in comparison to an equivalent patient population without preventive treatment.

The expression "treatment" or "therapy" means therapeutic treatment of patients having already developed one or more of said conditions in manifest, acute or chronic form, including symptomatic treatment in order to relieve symptoms of the specific indication or causal treatment in order to reverse or partially reverse the condition or to delay the progression of the indication as far as this may be possible, depending on the condition and the severity thereof. Thus the expression "treatment of a disease" as used herein means the management and care of a patient having developed the disease, condition or disorder. The purpose of treatment is to combat the disease, condition or disorder. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc. . . .) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

As used herein the term "prodrug" refers to (i) an inactive form of a drug that exerts its effects after metabolic processes within the body converting it to a usable or active form, or (ii) a substance that gives rise to a pharmacologically active metabolite, although not itself active (i.e. an inactive precursor).

The terms "prodrug" or "prodrug derivative" mean a covalently-bonded derivative, carrier or precursor of the parent compound or active drug substance which undergoes at least some biotransformation prior to exhibiting its pharmacological effect(s). Such prodrugs either have metabolically cleavable or otherwise convertible groups and are rapidly transformed in vivo to yield the parent compound, for example, by hydrolysis in blood or by activation via oxidation as in case of thioether groups. Most common prodrugs include esters and amide analogs of the parent compounds. The prodrug is formulated with the objectives of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). In general, prodrugs themselves have weak or no biological activity and are stable under ordinary conditions. Prodrugs can be readily prepared from the parent compounds using methods known in the art, such as those described in A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, particularly Chapter 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K. B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder et al. (eds.), Vol. 42, Academic Press, 1985, particularly pp. 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., M. Wolff (ed.), John Wiley & Sons, 1995, particularly Vol. 1 and pp. 172-178 and pp. 949-982; Pro-Drugs as Novel Delivery Systems, T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; Bioreversible Carriers in Drug Design, E. B. Roche (ed.), Elsevier, 1987, each of which is incorporated herein by reference in their entireties.

The term "pharmaceutically acceptable prodrug" as used herein means a prodrug of a compound of the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2"-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2.2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (−)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (−)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S. M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate salts) also comprise a part of the invention.

The term halogen generally denotes fluorine, chlorine, bromine and iodine.

The term "C_{1-n}-alkyl", wherein n is an integer selected from 2, 3, 4, 5 or 6, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_{1-5}-alkyl embraces the radicals H_3C—, H_3C—CH_2—, H_3C—CH_2—CH_2—, H_3C—$CH(CH_3)$—, H_3C—CH_2—CH_2—CH_2—, H_3C—CH_2—$CH(CH_3)$—, H_3C—$CH(CH_3)$—CH_2—, H_3C—$C(CH_3)_2$—, H_3C—CH_2—CH_2—CH_2—CH_2—, H_3C—CH_2—CH_2—$CH(CH_3)$—, H_3C—CH_2—$CH(CH_3)$—CH_2—, H_3C—$CH(CH_3)$—CH_2—CH_2—, H_3C—CH_2—$C(CH_3)_2$—, H_3C—$C(CH_3)_2$—CH_2—, H_3C—$CH(CH_3)$—$CH(CH_3)$— and H_3C—CH_2—$CH(CH_2CH_3)$—.

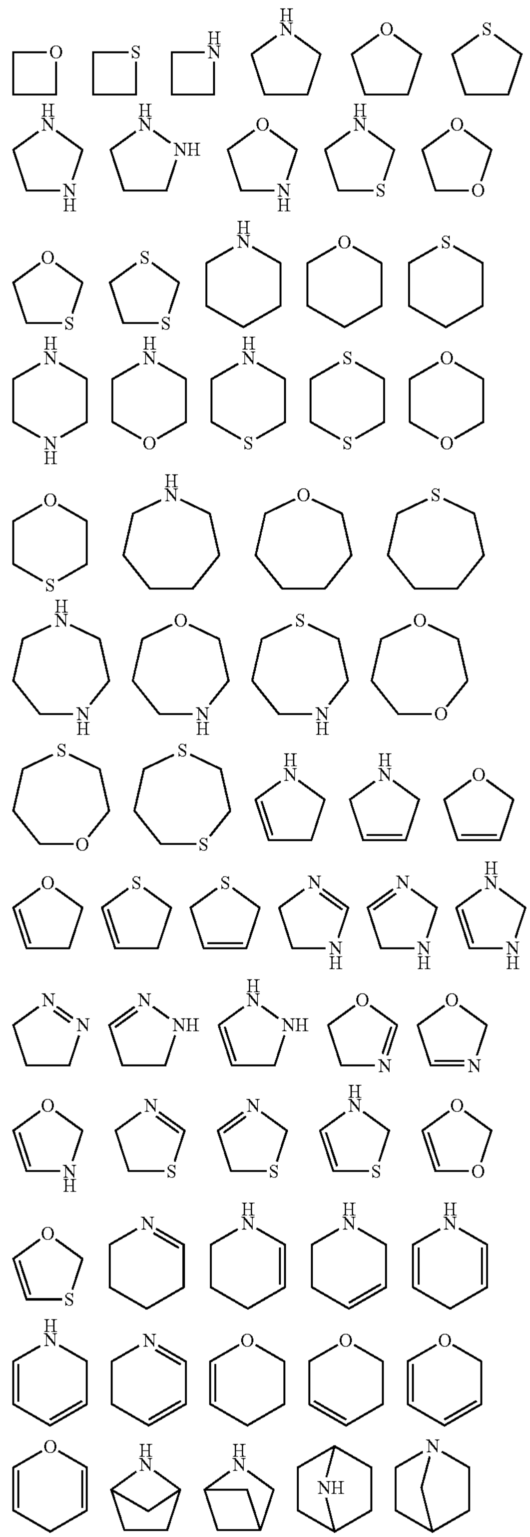
The term "C_{1-n}-alkylene" wherein n is an integer selected from 2, 3, 4, 5 or 6, preferably 4 or 6, either alone or in combination with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical containing from 1 to n carbon atoms. For example the term C_{1-4}-alkylene includes —CH_2—, —CH_2—CH_2—, —$CH(CH_3)$—, —CH_2—CH_2—CH_2—, —$C(CH_3)_2$—, —$CH(CH_2CH_3)$—, —$CH(CH_3)$—CH_2—, —CH_2—$CH(CH_3)$—, —CH_2—CH_2—CH_2—CH_2—, —CH_2—CH_2—$CH(CH_3)$—, —$CH(CH_3)$—CH_2—CH_2—, —CH_2—$CH(CH_3)$—CH_2—, —CH_2—$C(CH_3)_2$—, —$C(CH_3)_2$—CH_2—, —$CH(CH_3)$—$CH(CH_3)$—, —CH_2—$CH(CH_2CH_3)$—, —$CH(CH_2CH_3)$—CH_2—, —$CH(CH_2CH_2CH_3)$—, —$CH(CH(CH_3))_2$— and —$C(CH_3)(CH_2CH_3)$—.

The term "C_{3-n}-cycloalkyl", wherein n is an integer selected from 4, 5, 6, 7 or 8, preferably 4, 5 or 6, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to 8 C atoms. For example the term C_{3-8}-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

By the term "halo" added to a "alkyl", "alkylene" or "cycloalkyl" group (saturated or unsaturated) is such a alkyl or cycloalkyl group wherein one or more hydrogen atoms are replaced by a halogen atom selected from among fluorine, chlorine or bromine, preferably fluorine and chlorine, particularly preferred is fluorine. Examples include: H_2FC—, HF_2C—, F_3C—.

The term "aryl" as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second five- or six-membered, carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.

The term "C_{5-10}-heterocyclyl" means a saturated or unsaturated mono- or polycyclic-ring systems including aromatic ring system containing one or more heteroatoms independently selected from N, O or $S(O)_r$, wherein r=0, 1 or 2, consisting of 5 to 10 ring atoms wherein none of the heteroatoms is part of the aromatic ring. The term "heterocyclyl" is intended to include all the possible isomeric forms. Thus, the term "heterocyclyl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent (single or double) bond to any atom so long as appropriate valences are maintained:



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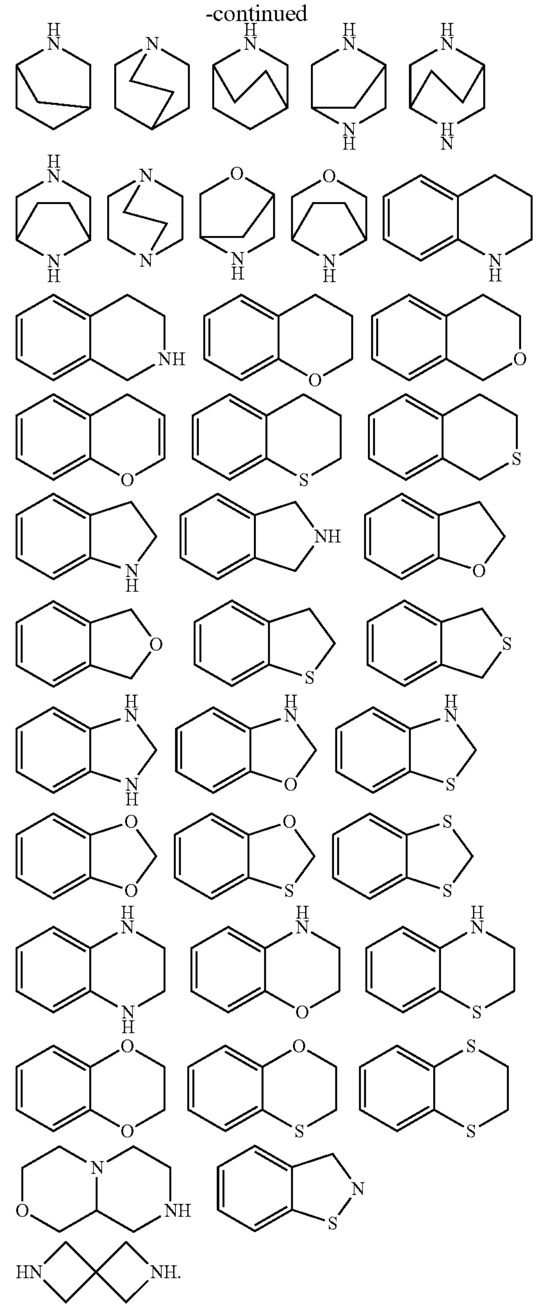
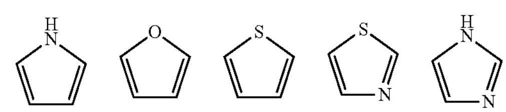


The term "C_{5-10}-heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms independently selected from N, O or $S(O)_r$, wherein r=0, 1 or 2, consisting of 5 to 10 ring atoms wherein at least one of the heteroatoms is part of aromatic ring. The term "heteroaryl" is intended to include all the possible isomeric forms. Thus, the term "heteroaryl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



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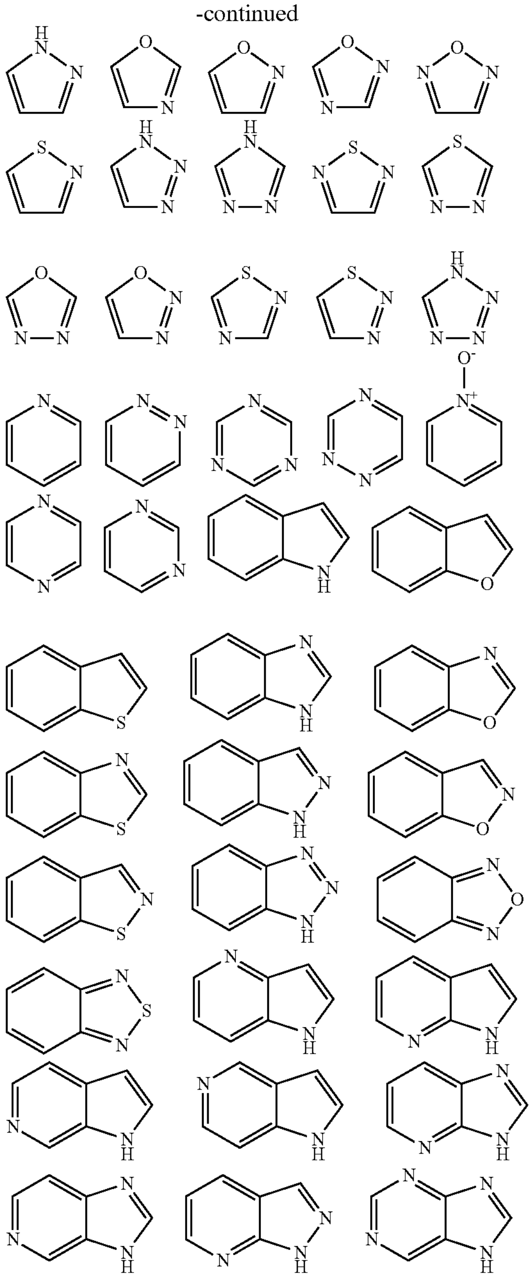

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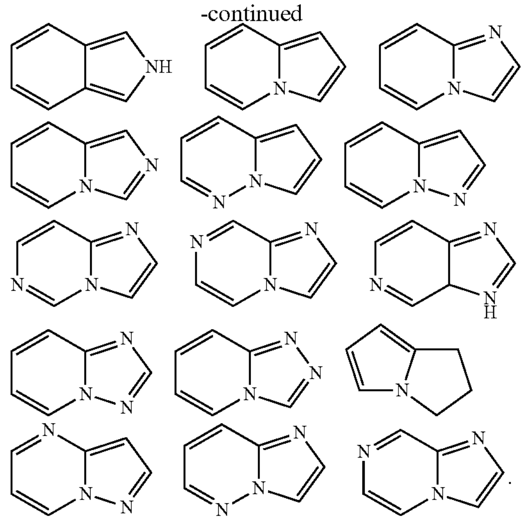


Preparation

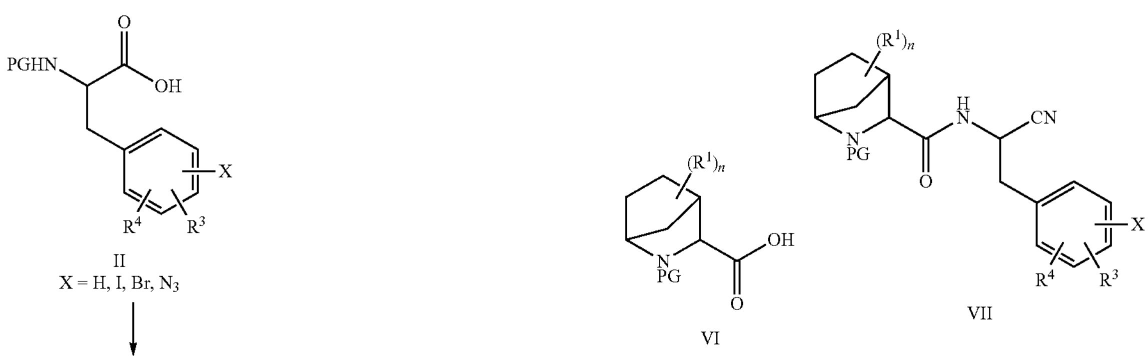
General Synthetic Methods

The invention also provides processes for making a compound of Formula I. In all methods, unless specified otherwise, R^1, R^2 and n in the formulas below shall have the meaning of R^1, R^2 and n in Formula 1 of the invention described herein above.

Optimal reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC) or LC-MS, if desired, and intermediates and products may be purified by chromatography on silica gel, HPLC and/or by recrystallization. The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the methods below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

A compound of Formula V, VII and IX may be made by the method outlined in Scheme 1:

Scheme 1



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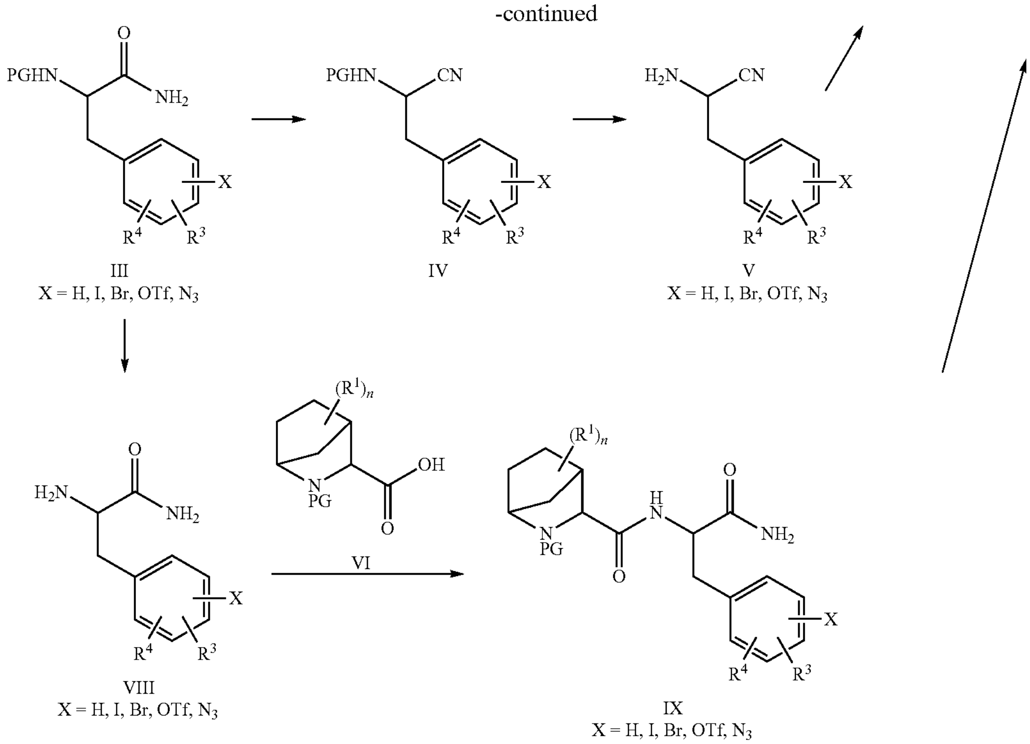


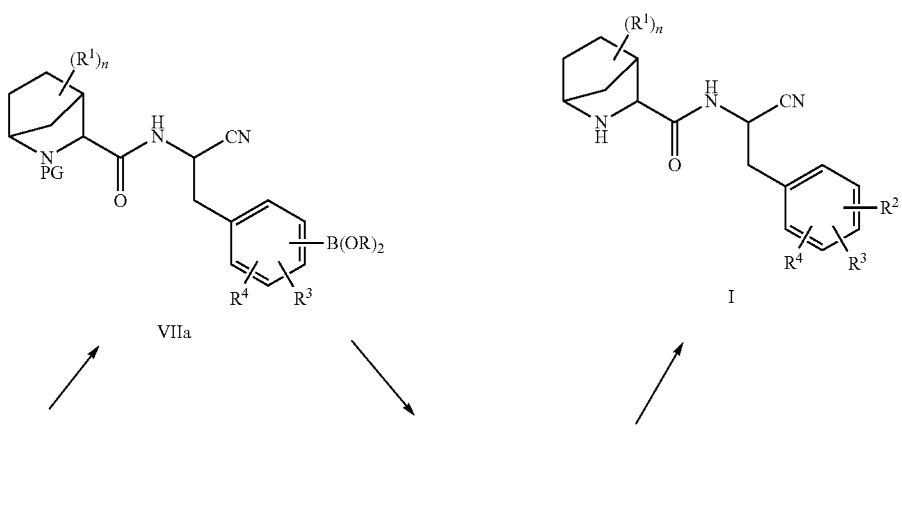
As illustrated in Scheme 1, a compound of Formula II, wherein PG represents a protecting group (e.g. tert-butoxycarbonyl), may be reacted with an aqueous ammonia solution, using standard literature procedures for the formation of an amide. For example, in the presence of a base such as N-methyl-morpholine or N-ethyl-morpholine and an activating agent such as O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumtetrafluoroborate (TBTU). The reaction is conveniently carried out in a suitable solvent such as N,N-dimethylformamide. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

Dehydration of an amide such as in a compound of Formula III or Formula IX to the corresponding nitrile of Formula IV or VII may be carried out by use of a dehydration agent such as (methoxycarbonylsulfamoyl)triethyl ammonium hydroxide, in a suitable solvent such as dichloromethane (DCM).

Reacting an acid of Formula VI using standard literature procedures for the formation of an amide, for example in the presence of a base such as N,N-diisopropylethylamine (DIPEA) and an activating agent such as HATU or TBTU, with an amine of Formula V or VIII in a suitable solvent, provides a compound of Formula VII or IX. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of tert-butoxycarbonyl, an acid such as formic acid, trifluoroacetic acid, p-toluenesulfonic acid or HCl may be used in a suitable solvent such as water, DCM or dioxane. Another method to deprotect tert-butoxycarbonyl is the reaction with trimethyliodosilane or trimethylchlorosilane in combination with sodium iodide in an appropriate solvent like acetonitrile, DMF or DCM.

Scheme 2



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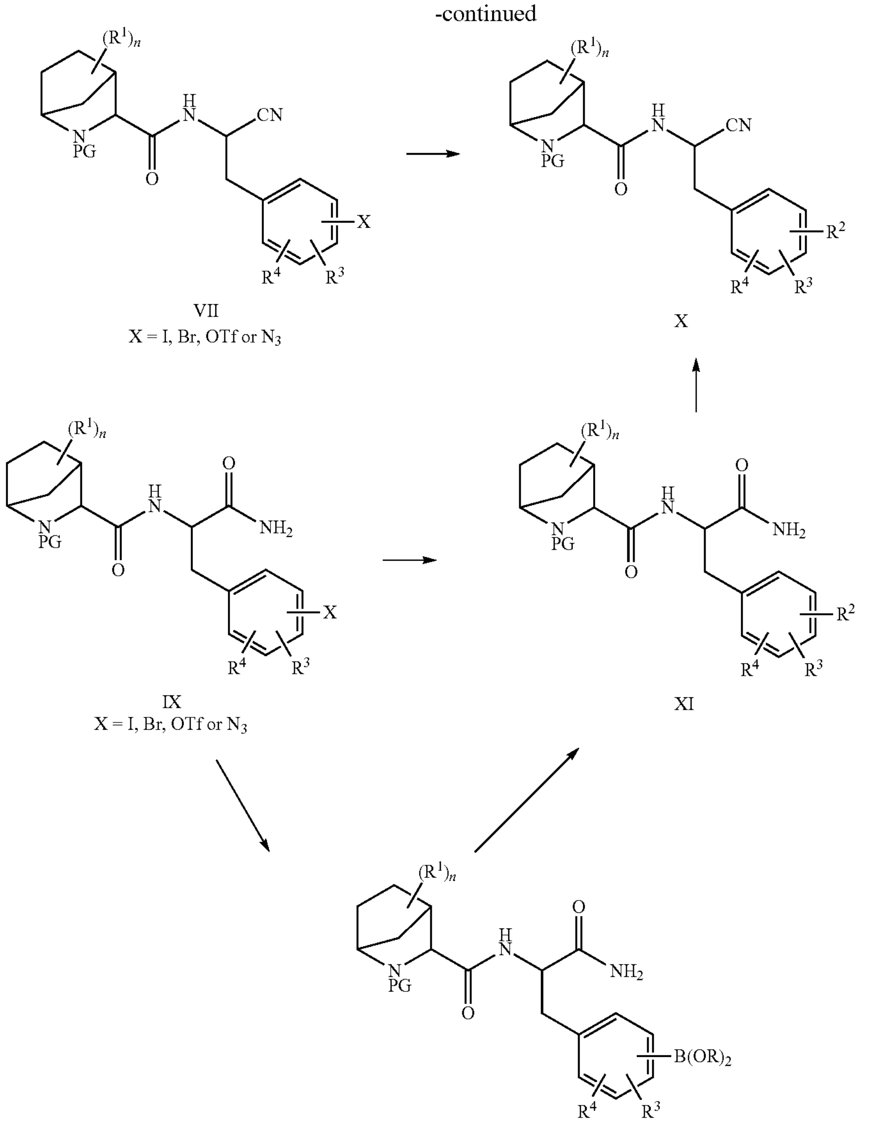


VII
X = I, Br, OTf or N_3

X

IX
X = I, Br, OTf or N_3

XI

IXa

During the reaction sequences depicted in Scheme 1 and Scheme 2 a hydroxy group (X═OH) can be converted to a trifluoromethanesulfonyl group (X═OTf) at any level. Especially, a compound IX with X═OH is transformed to the appropriate triflate (X═OTf) by reaction with N,N-bis-(trifluoromethanesulfonyl) aniline, or trifluoromethanesulfonyl chloride or anhydride, in the presence of an organic base e.g. triethylamine, morpholine, piperidine, DIPEA in an appropriate anhydrous solvent, e.g. DCM.

As illustrated in Scheme 2, (transition) metal catalyzed reaction of a compound of Formula VII or IX wherein X is I, Br, Cl or OTf, provides a compound of Formula X or XI. For example, reaction with a boronic acid or the corresponding boronic acid ester, in a suitable solvent such as acetonitrile, in the presence of a suitable catalyst such as 1,1-bis(di-tert-butylphosphino)ferrocene palladium dichloride and a suitable base such as K_2CO_3 provides a compound of Formula X or XI. Alternatively, reaction of a compound of Formula VII or IX, wherein X is I, Br, Cl or OTf with a tributyl(vinyl)tin reagent in the presence of a suitable catalyst such as bis-(triphenylphosphin)-palladiumchloride, in a suitable solvent such as dimethylformamide (DMF) and if desirable in the presence of an additive such as tetraethylammonium chloride provides compounds of Formula X or XI. Further, reaction of a compound of Formula VII or IX, wherein X is I or Br, may be reacted with an amine in the presence of a suitable catalyst such as Cu(I)I and a suitable base such as caesium carbonate and a suitable promotor such as L-proline provides a compound of Formula X or XI.

In an inversed fashion compounds of formula VII or IX (X: I, Br, Cl, OTf) can be converted into the corresponding boronic acid derivatives VIIa or IXa, wherein R can be H or lower alkyl independently and the residues R can form a ring. For example, VII or IX can be reacted with bis-pinacolato-diboron in the presence of a suitable catalyst such as 1,1-bis (di-tert-butylphosphino)ferrocene palladium dichloride and a suitable base such as potassium acetate or sodium, potassium or cesium carbonate or phosphate, in a suitable solvent such as dioxan, dimethylformamide (DMF), or dichloromethane (DCM) to yield the boronic esters VIIa or IXa, respectively.

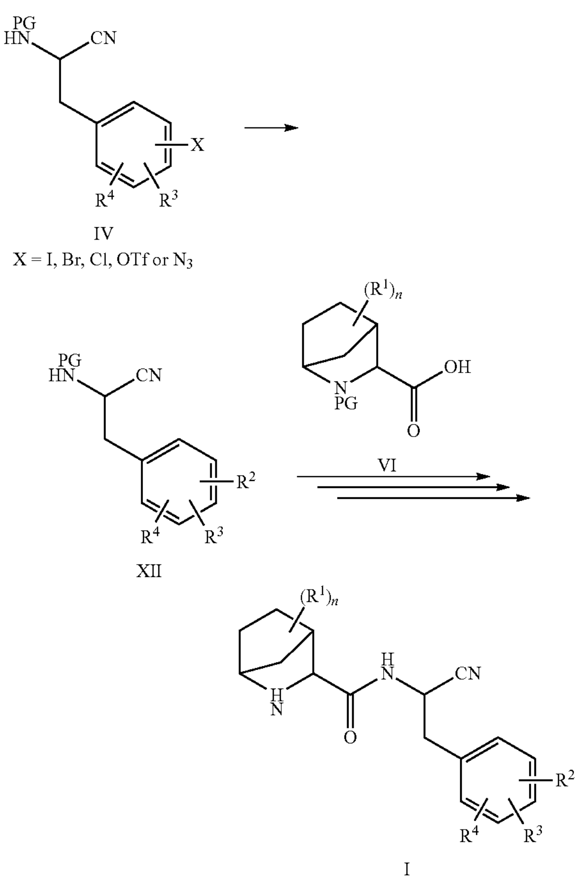
These can be reacted with appropriate aromatic halides in analogy as above to yield the desired coupling products of formula X or XI.

Further, as illustrated in Scheme 2, reaction of a compound of Formula VII or IX, wherein X is N_3 with an alkyne in the presence of a suitable catalyst such as copper(II)sulfate pentahydrate and a suitable reducing agent such as L-ascorbic acid in a suitable solvent such as dimethyl sulfoxide (DMSO)/water provides a compound of Formula X or XI.

Further modifications of compounds of Formula X, XI and I by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of the invention.

Dehydration of an amide of Formula XI to the corresponding nitrile of Formula X may be carried out by use of a dehydration agent such as (methoxycarbonylsulfamoyl)triethyl ammonium hydroxide, in a suitable solvent such as DCM.

Scheme 3

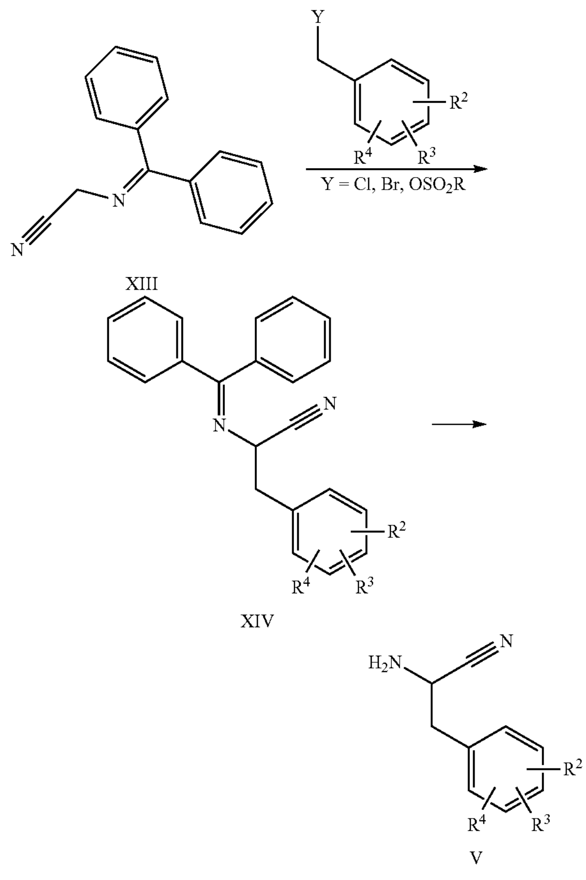


As illustrated in Scheme 3, (transition) metal catalyzed reaction of a compound of Formula IV wherein X is I, Br, Cl or OTf, provides a compound of Formula XII. For example, reaction with a boronic acid or the corresponding boronic acid ester, in a suitable solvent such as acetonitrile, in the presence of a suitable catalyst such as 1,1-bis(di-tert-butylphosphino)ferrocene palladium dichloride and a suitable base such as K_2CO_3 provides a compound of Formula XII.

An acid of Formula VI using standard literature procedures for the formation of an amide, for example in the presence of a base such as DIPEA and an activating agent such as HATU

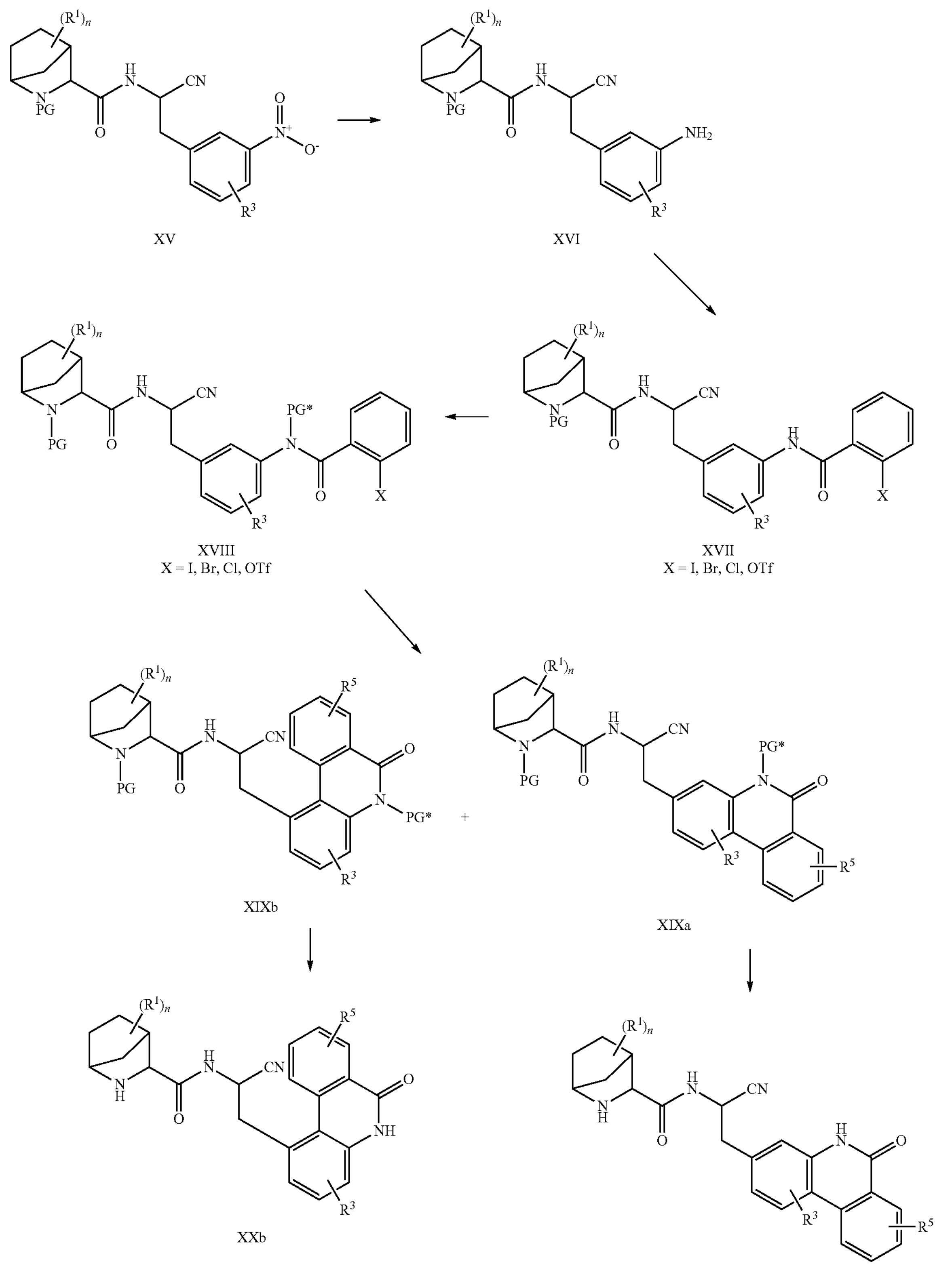
or TBTU, can be reacted with an amine of Formula XII in a suitable solvent. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses. Deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, for the deprotection of tert-butoxycarbonyl, an acid such as formic acid, p-toluenesulfonic acid, trifluoroacetic acid or HCl may be used in a suitable solvent such as water, DCM or dioxane and can be performed on the crude amide coupling product to provide a compound of Formula I. Another method to deprotect tert-butoxycarbonyl is the reaction with trimethyliodosilane or trimethylchlorosilane in combination with sodium iodide in an appropriate solvent like acetonitrile, DMF or DCM.

Scheme 4



As illustrated in Scheme 4, amino nitrile derivatives of Formula XIII can be converted to substituted amino nitriles of Formula V via alkylation to compounds of Formula XIV, followed by deprotection of the amino group. During the alkylation step a suitable base is used in an appropriate solvent, using a benzylation agent XV with an appropriate leaving group like Cl, Br, or sulfonates. Especially useful is the use of sodium hydroxide as base in water and DCM under phase transfer conditions using benzyltrimethylammonium chloride as described for example by Naidu et al, WO2011/46873. The protective group is removed under acidic conditions, e.g. aq. HCl in dioxan. The amino nitrile V is further processed as depicted in Scheme 1.

Scheme 5



As illustrated in Scheme 5, nitro compounds of formula XV can be reduced to anilines of formula XVI by catalytic hydrogenation under conditions, where the nitrile group is still stable. Better suited are reagents like sodium dithionite,

$SnCl_2$ or iron in a suitable solvent like water, methanol, ethanol, acetonitrile or ethyl acetate.

Reacting of 2-halo-benzoic acid, especially 2-iodo-benzoic acid using standard literature procedures for the formation of an amide, for example in the presence of a base such as N,N-diisopropylethylamine (DIPEA) and an activating agent such as HATU or TBTU, with an amine of Formula XVI in a suitable solvent, provides a compound of Formula XVII. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses.

The benzoic amide group as in Formula XVII can be protected by an acid labile group, especially by alkoxymethyl or silylalkoxymethyl groups as mentioned for example in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. Especially useful is the use of 2-trimethylsilylethoxymethylchloride as alkylating agent after having removed the amide proton by a strong base such as NaH in an inert solvent like DMF, THF or dioxan. The products are compounds of the formula XVIII.

Cyclisation of compounds like formula XVIII can be performed with the aid of a palladium catalyst like $Pd(PPh_3)_4$ (tetrakis(triphenylphosphine)palladium(0) and a base like potassium acetate or sodium, potassium or cesium carbonate or phosphate, especially sodium carbonate in a suitable solvent, e.g. DMF, preferrably under elevated temperature. This results in the formation of compound of the formula XIXa and XIXb, which can be separated or processed further as a mixture.

Compounds like XIXa or XIXb or a mixture thereof can be deprotected in acidic medium. Deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', T. W. Greene and P. G. M. Wuts, Wiley-Interscience. For example, an acid such as formic acid, p-toluenesulfonic acid, trifluoroacetic acid or HCl may be used in a suitable solvent such as water, DCM or dioxane and can be performed on the crude amide coupling product to provide a compound of Formula XXa and XXb. Another method to deprotect first the tert-butoxycarbonyl is the reaction with trimethyliodosilane or trimethylchlorosilane in combination with sodium iodide in an appropriate solvent like acetonitrile, DMF or DCM. After that the trimethylsilylmethoxymethyl group can be removed in acidic medium as mentioned above, especially with formic acid again leading to compounds of the formula XXa and XXb.

SYNTHETIC EXAMPLES

The following are representative compounds of the invention which can be made by the general synthetic schemes, the examples, and known methods in the art. Starting materials and intermediates were either commercially available and purchased from catalogues of AATPHARM, ABCR, ACROS, ACTIVATE, ALDRICH, ALFA, ALLICHEM, ANICHEM, ANISYN, ANISYN Inc., APAC, APOLLO, APOLLO-INTER, ARKPHARM, ARKPHARMINC, ASIBA PHARMATECH, ATOMOLE, BACHEM, BEPHARM, BIOFOCUS, BIOGENE, BORON-MOL, BOROPHARM, CHEMBRIDGE, CHEMCOLLECT, CHEMFUTURE, CHEMGENX, CHEMIMPEX, CHESS, COMBI-BLOCKS, COMBI-PHOS, DLCHIRAL, EGA, E-MERCK, EMKA-CHEMIE, ENAMINE, EPSILON, FLROCHEM, FLUKA, FOCUS, FRONTIER, ISOCHEM, JW PHARMLAB, KINGSTONCHEM, LANCASTER, MANCHESTER, MANCHESTER ORGANICS, MAYBRIDGE, MAYBR-INT, MERCACHEM, MERCK, MILESTONE, MOLBRIDGE, NETCHEM, OAKWOOD, PHARMABRIDGE, PLATTE, RIEDEL DE HAEN, SMALL-MOL, SPECS, SPECTRA GROUP LIMITED, INC, SYNCHEM OHG, SYNCHEM-INC, SYNCOM, TCI, VIJAYA PHARMA, WAKO, WUXIAPPTEC or were synthesized according to literature or as described below in "Synthesis of starting materials/educts"

"Liquid chromatography-mass spectroscopy (LCMS) retention time and observed m/z data for the compounds below are obtained by one of the following methods:

LC-MS Method 001_CA07

Device-Description	Waters Acquity with DAD and MSD
Column	Waters Sunfire C18
Column Dimension	2.1 × 50 mm
Particle Size	2.5 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% TFA]	% Sol [Acetonitrile 0.08% TFA]	Flow [ml/min]	Temp [° C.]
0.0	95.0	5.0	1.5	60.0
0.75	0.0	100.0	1.5	60.0
0.85	0.0	100.0	1.5	60.0

LC-MS Method 002_CA03

Device-Description	Agilent 1100 with DAD and MSD
Column	Waters Sunfire C18
Column Dimension	3.0 × 30 mm
Particle Size	2.5 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% TFA]	% Sol [Acetonitrile	Flow [ml/min]	Temp [° C.]
0.0	99.0	1.0	2.0	60.0
0.9	0.0	100.0	2.0	60.0
1.1	0.0	100.0	2.0	60.0

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LC-MS Method 002_CA07	
Device-Description	Waters Acquity with 3100 MS
Column	Waters XBridge BEH C18
Column Dimension	3.0 × 30 mm
Particle Size	1.7 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% NH4OH]	% Sol [Acetonitrile	Flow [ml/min]	Temp [° C.]
0.0	95.0	5.0	1.5	60 0
0.7	0.1	99.9	1.5	60.0
0.8	0.1	99.9	1.5	60.0
0.81	95.0	5.0	1.5	60.0
1.1	95.0	5.0	1.5	60.0

LC-MS Method 003_CA04	
Device-Description	Agilent 1100 with DAD and MSD
Column	Waters XBridge C18
Column Dimension	3.0 × 30 mm
Particle Size	2.5 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% NH4OH]	% Sol [Acetonitrile	Flow [ml/min]	Temp [° C.]
0.0	98.0	2.0	2.0	60.0
1.2	0.0	100.0	2.0	60.0
1.4	0.0	100.0	2.0	60.0

LC-MS Method 004_CA01	
Device-Description	Agilent 1100 with DAD, Waters Autosampler and MSD
Column	Waters Sunfire C18
Column Dimension	4.6 × 30 mm
Particle Size	3.5 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% TFA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [° C.]
0.0	98.0	2.0	2.5	60.0
1.5	0.0	100.0	2.5	60.0
1.8	0.0	100.0	2.5	60.0

LC-MS Method 004_CA05	
Device-Description	Waters Acquity with DAD and MSD, CTC Autosampler
Column	Waters XBridge C18
Column Dimension	3.0 × 30 mm
Particle Size	2.5 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% NH_4OH]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [° C.]
0.0	98.0	2.0	2.0	60.0
1.2	0.0	100.0	2.0	60.0
1.4	0.0	100.0	2.0	60.0

LC-MS Method 004_CA07	
Device-Description	Waters Acquity with with 3100 MS
Column	YMC Triart C18
Column Dimension	2.0 × 30 mm
Particle Size	1.9 μm

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% NH4OH]	% Sol [Acetonitrile	Flow [ml/min]	Temp [° C.]
0.0	95.0	5.0	1.5	60.0
0.75	0.1	99.9	1.5	60.0
0.8	0.1	99.9	1.5	60 0
0.81	95.0	5.0	1.5	60.0
1.1	95.0	5.0	1.5	60.0

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LC-MS Method 005_CA01				
Device-Description	Agilent 1100 with DAD, Waters Autosampler and MS-Detector			
Column	Waters Sunfire C18			
Column Dimension	3.0 × 30 mm			
Particle Size	2.5 µm			

Gradient/Solvent Time [min]	% Sol [H_2O 0.1% TFA]	% Sol [Acetonitrile	Flow [ml/min]	Temp [° C.]
0.0	98.0	2.0	2.0	60.0
1.2	0.0	100.0	2.0	60.0
1.4	0.0	100.0	2.0	60.0

LC-MS Method V001_003				
Device-Description	Waters Alliance with DAD and MSD			
Column	Waters XBridge C18			
Column Dimension	4.6 × 30 mm			
Particle Size	3.5 µm			

Gradient/Solvent Time [min]	% Sol [H2O, 0.1% TFA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	95	5	4	60
0.20	95	5	4	60
1.5	0	100	4	60
1.75	0	100	4	60

LC-MS Method V001_007				
Device-Description	Waters Alliance with DAD and MSD			
Column	Waters XBridge C18			
Column Dimension	4.6 × 30 mm			
Particle Size	3.5 µm			

Gradient/Solvent Time [min]	% Sol [H2O, 0.1% TFA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	95	5	4	60
1.6	0	100	4	60
1.85	0	100	4	60
1.9	95	5	4	60

LC-MS Method V003_003				
Device-Description	Waters Alliance with DAD and MSD			
Column	Waters XBridge C18			
Column Dimension	4.6 × 30 mm			
Particle Size	3.5 µm			

Gradient/Solvent Time [min]	% Sol [H_2O, 0.1% NH_3]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	95	5	4	60
0.2	95	5	4	60
1.5	0	100	4	60
1.75	0	100	4	60

LC-MS Method V011_S01				
Device-Description	Waters Alliance with DAD and MSD			
Column	Waters XBridge C18			
Column Dimension	4.6 × 30 mm			
Particle Size	3.5 µm			

Solvent Gradient time [min]	% Sol [H_2O, 0.1% NH_3]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	97	3	5	60
0.2	97	3	5	60
1.6	0	100	5	60
1.7	0	100	5	60

-continued

LC-MS Method V012_S01	
Device-Description	Waters Alliance with DAD and MSD
Column	Waters XBridge C18
Column Dimension	4.6 × 30 mm
Particle Size	3.5 μm

Solvent Gradient time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	97	3	5	60
0.2	97	3	5	60
1.6	0	100	5	60
1.7	0	100	5	60

LC-MS Method V018_S01	
Device-Description	Waters Alliance with DAD and MSD
Column	Waters Sunfire C18
Column Dimension	4.6 × 30 mm
Particle Size	3.5 μm

Solvent Gradient time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	97	3	5	60
0.2	97	3	5	60
1.6	0	100	5	60
1.7	0	100	5	60

LC-MS Method W018_S01	
Device-Description	Waters 1525 with DAD and MSD
Column	Waters Sunfire C18
Column Dimension	4.6 × 30 mm
Particle Size	2.5 μm

Solvent Gradient time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	97	3	4	60
0.15	97	3	3	60
2.15	0	100	3	60
2.20	0	100	4.5	60
2.40	0	100	4.5	60

LC-MS Method X001_002	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters XBridge BEH C18
Column Dimension	2.1 × 30 mm
Particle Size	1.7 μm

Gradient/Solvent Time [min]	% Sol [H_2O, 0.10% TFA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	99	1	1.3	60
0.05	99	1	1.3	60
1.05	0	100	1.3	60
1.2	0	100	1.3	60

LC-MS Method X001_004	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters XBridge C18
Column Dimension	2.1 × 20 mm
Particle Size	2.5 μm

Gradient/Solvent Time [min]	% Sol [H_2O, 0.10% TFA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	95	5	1.4	60
0.05	95	5	1.4	60
1.00	0	100	1.4	60
1.1	0	100	1.4	60

-continued

LC-MS Method X002_002	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters Sunfire C18
Column Dimension	2.1 × 30 mm
Particle Size	2.5 μm

Gradient/ Solvent Time [min]	% Sol [H2O, 0.10% TFA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.00	99	1	1.2	60
0.15	99	1	1.2	60
1.10	0	100	1.2	60
1.25	0	100	1.2	60

LC-MS Method X011_S02	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters XBridge BEH C18
Column Dimension	2.1 × 30 mm
Particle Size	1.8 μm

Solvent Gradient time [min]	% Sol [H2O, 0.1% NH3]	% Sol [Acetonitril]	Flow [rnl/min]	Temp [° C.]
0.00	99	1	1.3	60
0.02	99	1	1.3	60
1.00	0	100	1.3	60
1.10	0	100	1.3	60

LC-MS Method X011_S03	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters Xbridge BEH C18
Column Dimension	2.1 × 30 mm
Particle Size	1.7 μm

Solvent Gradient time [min]	% Sol [H2O, 0.1% NH3]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.00	95	5	1.3	60
0.02	95	5	1.3	60
1.00	0	100	1.3	60
1.10	0	100	1.3	60

LC-MS Method X012_S01	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters XBridge BEH C18
Column Dimension	2.1 × 30 mm
Particle Size	1.7 μm

Solvent Gradient time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	99	1	1.6	60
0.02	99	1	1.6	60
1.00	0	100	1.6	60
1.10	0	100	1.6	60

LC-MS Method X012_S02	
Device-Description	Waters Acquity with DAD and MSD
Column	Waters XBridge BEH C18
Column Dimension	2.1 × 30 mm
Particle Size	1.7 μm

Solvent Gradient time [min]	% Sol [H2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	99	1	1.3	60
0.02	99	1	1.3	60
1.00	0	100	1.3	60
1.10	0	100	1.3	60

-continued

LC-MS Method X016_S01				
Device-Description		Waters Acquity with DAD and MSD		
Column		Waters XBridge BEH Phenyl		
Column Dimension		2.1 × 30 mm		
Particle Size		1.7 µm		
Solvent Gradient time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	99	1	1.6	60
0.02	99	1	1.6	60
1.00	0	100	1.6	60
1.10	0	100	1.6	60

LC-MS Method X018_S01				
Device-Description		Waters Acquity with DAD and MSD		
Column		Waters Sunfire C18		
Column Dimension		2.1 × 30 mm		
Particle Size		2.5 µm		
Gradient/Solvent Time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	99	1	1.5	60
0.02	99	1	1.5	60
1.00	0	100	1.5	60
1.10	0	100	1.5	60

LC-MS Method X018_S02				
Device-Description		Waters Acquity with DAD and MSD		
Column		Waters Sunfire C18		
Column Dimension		2.1 × 30 mm		
Particle Size		2.5 µm		
Gradient/Solvent Time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.0	99	1	1.3	60
0.02	99	1	1 3	60
1.00	0	100	1.3	60
1.10	0	100	1.3	60

LC-MS Method Z001_002				
Device-Description		Agilent 1200 with DAD and MSD		
Column		Waters XBridge C18		
Column Dimension		3 × 30 mm		
Particle Size		2.5 µm		
Gradient/Solvent Time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	95	5	2.2	60
0.05	95	5	2.2	60
1.40	0	100	2.2	60
1.80	0	100	2.2	60

LC-MS Method Z011_S03				
Device-Description		Agilent 1200 with DAD and MSD		
Column		Waters XBridge C18		
Column Dimension		3 × 30 mm		
Particle Size		2.5 µm		
Gradient/Solvent Time [mm]	% Sol [H_2O, 0.1% NH3]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

-continued

LC-MS Method Z011_U03				
Device-Description	Agilent 1200 with DAD and MSD			
Column	Waters XBridge C18			
Column Dimension	3 × 30 mm			
Particle Size	2.5 μm			
Gradient/Solvent Time [min]	% Sol [H_2O, 0.1% NH3]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.00	50	50	2.2	60
0.20	50	50	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method Z012_S04				
Device-Description	Agilent 1200 with DAD and MSD			
Column	Waters XBridge C18			
Column Dimension	3 × 30 mm			
Particle Size	2.5 μm			
Gradient/Solvent Time [min]	% Sol [H_2O, 0.1% NH3]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method Z018_S04				
Device-Description	Agilent 1200 with DAD and MSD			
Column	Waters Sunfire C18			
Column Dimension	3 × 30 mm			
Particle Size	2.5 μm			
Solvent Gradient time [min]	% Sol [H_2O, 0.1% TFA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method Z020_S01				
Device-Description	Agilent 1200 with DAD and MSD			
Column	Waters Sunfire C18			
Column Dimension	3 × 30 mm			
Particle Size	2.5 μm			
Solvent Gradient time [min]	% Sol [H_2O, 0.1% FA]	% Sol [Acetonitril]	Flow [ml/min]	Temp [° C.]
0.00	97	3	2.2	60
0.20	97	3	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

LC-MS Method V001_007				
Device-Description	Waters Alliance with DA- and MS-Detector			
Column	XBridge C18			
Column Dimension	4.6 × 30 mm			
Particle Size	3.5 μm			
Solvent Gradient time [min]	% Sol [H_2O, 0.1% FA]	% Sol [Methanol]	Flow [ml/min]	Temp [° C.]
0.0	95	5	4.0	60
1.6	0	100	4.0	60
1.85	0	100	4.0	60
1.9	95	5	4.0	60

-continued

LC-MS Method I_ADH_15_MEOH_DEA.M	
Device-Description	Agilent 1260 SFC with DAD
Column	Daicel Chiralpak AD-H
Column Dimension	4.6 × 250 mm
Particle Size	5 μm

Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [Methanol, 0.2% Diethylamine]	Flow [ml/min]	Temp [° C.]	Backpressure [bar]
0.00	85	15	4	40	150
10.00	85	15	4	40	150

LC-MS Method I_OJH_10_IPROP_DEA.M	
Device-Description	Agilent 1260 SFC with DAD
Column	Daicel Chiralcel OJ-H
Column Dimension	4.6 × 250 mm
Particle Size	5 μm

Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [Isopropanol, 0.2% Diethylamine]	Flow [ml/min]	Temp [° C.]	Backpressure [bar]
0.00	90	10	4	40	150
10.00	90	10	4	40	150

LC-MS Method I_IC_20_MEOH_NH3.M	
Device-Description	Agilent 1260 SFC with DAD and MSD
Column	Daicel Chiralpak IC
Column Dimension	4.6 × 250 mm
Particle Size	5 μm

Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [20 rnM NH3 in Methanol]	Flow [ml/min]	Temp [° C.]	Backpressure [bar]
0.00	80	20	4	40	150
10.00	80	20	4	40	150

LC-MS Method I_ADH_40_MEOH_DEA.M	
Device-Description	Agilent 1260 SFC with DAD
Column	ID aicel Chiralpak AD-H
Column Dimension	4.6 × 250 mm
Particle Size	5 μm

Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [Methanol, 0.2% Diethylamine]	Flow [ml/min]	Temp [° C.]	Backpressure [bar]
0.00	60	40	4	40	150
10.00	60	40	4	40	150

LC-MS Method I_ASH_30_10MIN_SS4P.M	
Device-Description	Berger SFC Analytix with DAD
Column	Daicel Chiralpak AS-H
Column Dimension	4.6 × 250 mm
Particle Size	5 μm

Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [Ethanol, 0.2% Diethylamine]	Flow [ml/min]	Temp [° C.]	Backpressure [bar]
0.00	70	30	4	40	120
10.00	70	30	4	40	120

-continued

LC-MS Method I_OJH_10_MEOH_DEA.M					
Device-Description		Agilent 1260 SFC with DAD			
Column		Daicel Chiralcel OJ-H			
Column Dimension		4.6 × 250 mm			
Particle Size		5 μm			
Solvent Gradient time [min]	% Sol [$scCO_2$]	% Sol [Methanol, 0.2% Diethylamine]	Flow [ml/min]	Temp [° C.]	Backpressure [bar]
0.00	90	10	4	40	150
10.00	90	10	4	40	150

Mixture of stereoisomers can be separated on preparative scale by one of the following chiral SFC methods. 2x describes two columns switched in a row.

Methode: Chiral SFC A
Column: 2x Daicel Chiralpak AD-H 5 μm 20×250 mm
Eluent: 85% $scCO_2$, 15% Methanol 0.2% Diethylamine
Flow: 55 mL/min
Temperature: 40° C.
Backpressure: 120 bar
Wavelength: 254 nm
Concentration: 52 mg/ml in Methanol
Injection volume: 300 μl
Device-Description: Thar MultiGram II

Methode: Chiral SFC B
Column: 2x Chiralcel OJ-H 5 μm, 20×250 mm
Eluent: 90% $scCO_2$, 10% Isopropanol 0.2% Diethylamine
Flow: 60 mL/min
Temperature: 40° C.
Backpressure: 150 bar
Wavelength: 254 nm
Concentration: 50 mg/ml in Methanol
Injection volume: 200 μl
Device-Description: Jasco Rockclaw 150

Methode: Chiral SFC C
Column: 2x Daicel Chiralpak AD-H 5 μm, 10×250 mm
Eluent: 85% $scCO_2$, 15% Methanol 0.2% Diethylamine
Flow: 10 mL/min
Temperature: 40° C.
Backpressure: 120 bar
Wavelength: 254 nm
Concentration: 15 mg/ml in Methanol
Injection volume: 100 μl
Device-Description: Thar MiniGram

Methode: Chiral SFC D
Column: 1x Daicel Chiralpak AD-H, 5 μm, 20×250 mm
Eluent: 60% $scCO_2$, 40% Methanol 0.2% Diethylamine
Flow: 60 mL/min
Temperature: 40° C.
Backpressure: 120 bar
Wavelength: 254 nm
Concentration: 50 mg/ml in Methanol
Injection volume: 400 μl
Device-Description: Thar MultiGram II

Methode: Chiral SFC E
Column: 2x Daicel Chiralpak AS-H 5 μm, 20×250 mm
Eluent: 70% CO_2, 30% Ethanol 0.2% Diethylamine
Flow: 55 mL/min
Temperature: 40° C.
Backpressure: 120 bar
Wavelength: 254 nm
Concentration: 100 mg/ml in Methanol
Injection volume: 200 μl
Device-Description: Thar MultiGram II

Methode: Chiral SFC F
Column: Daicel Chiralpak IC 5 μm, 20×250 mm
Eluent: 85% $scCO_2$, 15% Ethanol
Flow: 60 mL/min
Temperature: 40° C.
Backpressure: 150 bar
Wavelength: 254 nm
Concentration: 35 mg/ml in Methanol
Injection volume: 500 μl
Device-Description: Sepiatec Prep SFC 100

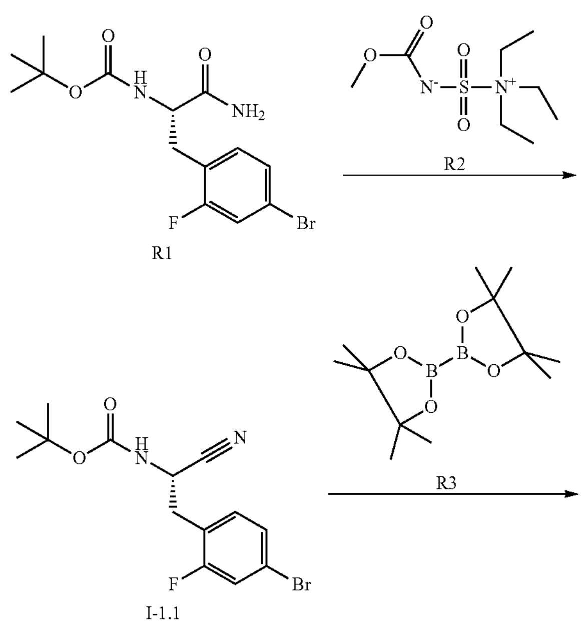
Methode: Chiral SFC G
Column: Chiralpak AY-10 μm, 50×300 mm
Eluent: A for CO_2, and B for ethanol: n-heptane=1:1
Gradient: B 10%
Flow: 170 mL/min
Temperature: 38° C.
Backpressure: 100 bar
Wavelength: 220 nm
Concentration: 300 mg/ml in ethanol
Injection volume: 4 mL per injection
Cycletime: 3.5 min
Device-Description: Thar 200 preparative SFC

Synthesis Methods:

Method A

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-(2-methylisoindolin-5-yl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 1



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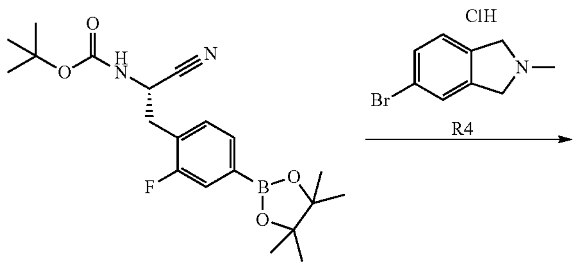
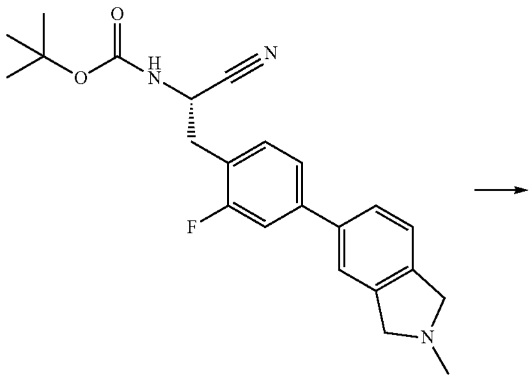
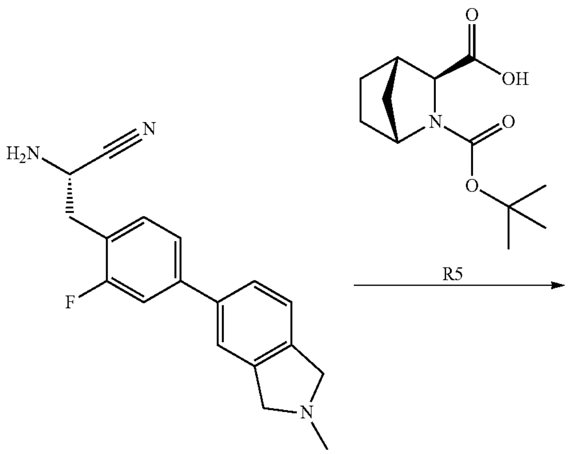


I-1.2



I-1.3



I-1.4

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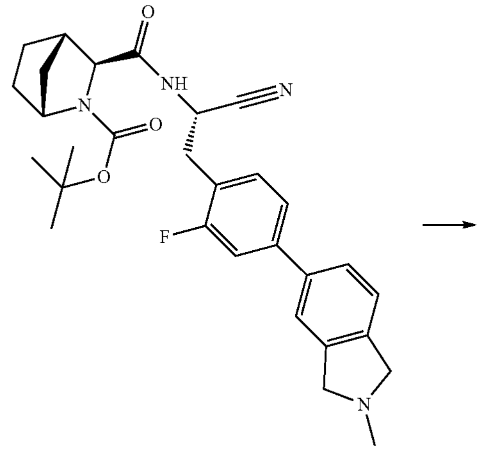
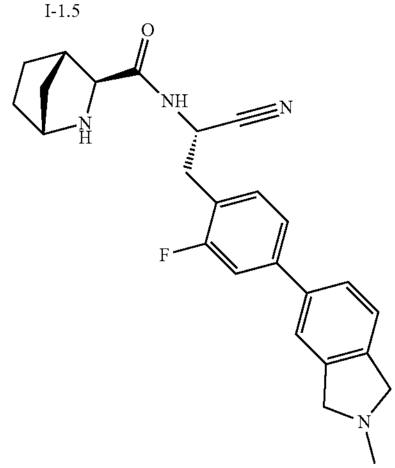


I-1.5



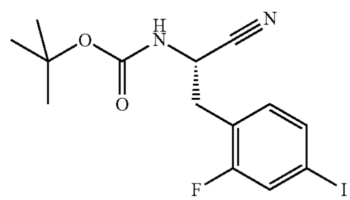
Example 1

Step 1: Synthesis of Intermediate I-1.1

R1 (20.0 g, 55 mmol) is suspended in DCM (400 mL) and a solution of R2 (26.4 g, 111 mmol) dissolved in DCM is added. The reaction mixture is stirred for 12 h under argon atmosphere. The reaction mixture is washed with water. The organic layer is dried over $MgSO_4$, filtrated and concentrated. The residue is dissolved in DCM, filtrated by flash chromatography (using solvent mixture cyclohexane/ethyl acetate=70/30) and concentrated to give I-1.1. Yield 97% m/z 287/343 [M+H]+, rt 1.29 min, LC-MS Method X012_S01.

The following intermediate as shown in Table 2 is synthesized in a similar fashion from the appropriate intermediates:

TABLE 2

Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-1.1.1	R1.1		391	1.29	V012_S01

Step 2: Synthesis of Intermediate I-1.2

To I-1.1 (5.80 g, 17 mmol) in anhydrous dioxane (60 mL) R3 (5.20 g, 20 mmol) and potassium acetate (4.98 g, 51 mmol) are added. The mixture is purged with argon, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2$(dppf)) (1.38 g, 1.7 mmol) is added to the mixture and heated to 80° C. for 2 h. DCM is added and the mixture is filtrated. The filtrate is diluted with water and extracted with DCM. The organic layer is dried over $MgSO_4$, filtrated and concentrated. The residue is purified by flash chromatography (cyclohexane/ethyl acetate=8/2) and concentrated. Yield 97% m/z 291/335/391 [M+H]+, rt 1.36 min, LC-MS Method V012_S01.

Step 3: Synthesis of Intermediate I-1.3

I-1.2 (1.22 g, 5 mmol) and R4 (2.30 g, 5.9 mmol) are dissolved in acetonitrile (25 mL). Na_2CO_3-solution (2 mol/L, 4.9 mL) and 1,1'-Bis(di-tert-butylphosphino)ferrocene-palladium dichloride (319 mg, 0.49 mmol) are added. The reaction mixture is stirred at 80° C. for 1 h. The crude mixture is extracted with ethyl acetate, washed with half saturated brine. The organic layer is dried over $MgSO_4$, filtrated and concentrated and the residue is purified by reversed phase HPLC. Yield 59%, m/z=396 [M+H]+, rt 0.96 min, LC-MS Method V012_S01.

The following intermediates as shown in Table 3 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 3

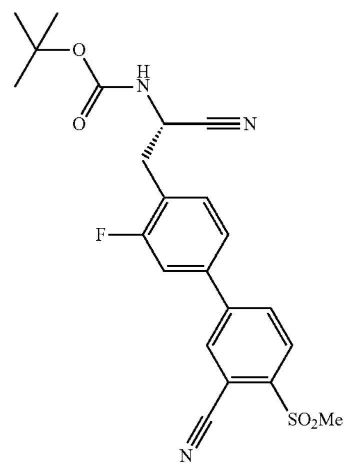
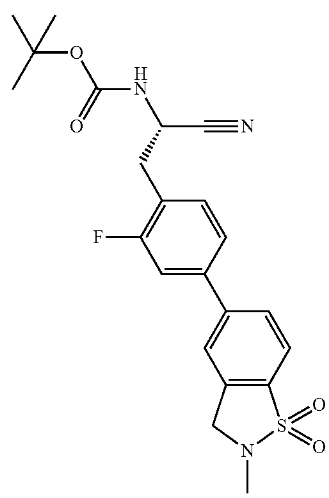
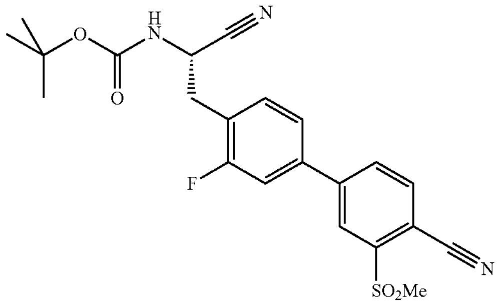
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-1.3.1	I-1.1.1, direct coupling with boronic ester R7.3		444	1.21	V018_S01
I-1.3.2	I-1.2		446	1.18	V012_S01

TABLE 3-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-1.3.3	I-1.1, direct coupling with boronic ester R7.1		444	1.14	V011_S01

Step 4: Synthesis of Intermediate I-1.4

I-1.3 (1.15 g, 2.91 mmol) is dissolved in acetonitrile. 1.39 g p-toluenesulfonic acid monohydrate is added and stirred for 48 h. The precipitate is filtered off, dissolved in ethyl acetate and washed with saturated $NaHCO_3$-solution. The organic layer is dried over $MgSO_4$, filtrated and concentrated. Yield 78%. m/z 296 [M+H]+, rt 1.03 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 4 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 4

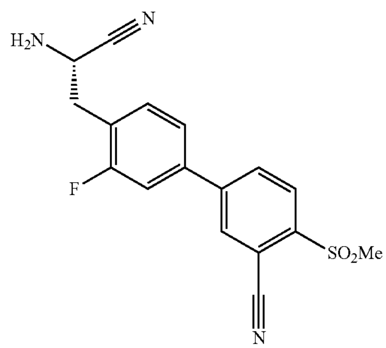
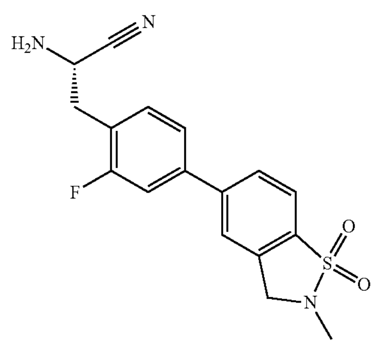
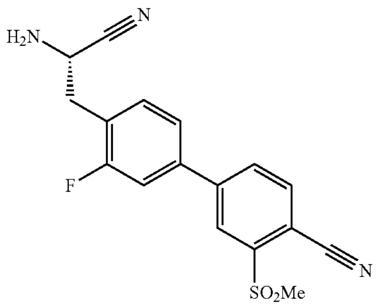
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-1.4.1	I-1.3.1		344	0.76	V018_S01
I-1.4.2	I-1.3.2		346	0.96	V011_S01

TABLE 4-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-1.4.3	I-1.3.3		344	0.77	V018_S01

Step 5: Synthesis of Intermediate I-1.5

To R5 (purchased from Aldrich or synthesized in analogy to Tararov et al, Tetrahedron Asymmetry 13 (2002), 25-28) (98 mg, 0.4 mmol) in DMF (1.5 mL) diisopropylethylamine (0.18 mL, 1.0 mmol) and HATU (154 mg, 0.4 mmol) are added and the reaction mixture is stirred for 15 min. Then intermediate I-1.4 (100 mg, 0.3 mmol) is added and the mixture is stirred for 12 h. DCM is added and the mixture is washed with saturated Na2CO3 solution. The organic layer is dried over $MgSO_4$, filtrated, and the residue is concentrated. Then the residue is purified by reversed phase HPLC. Yield 68%, m/z 419/463/518 [M+H]+, rt 1.29 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 5 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 5

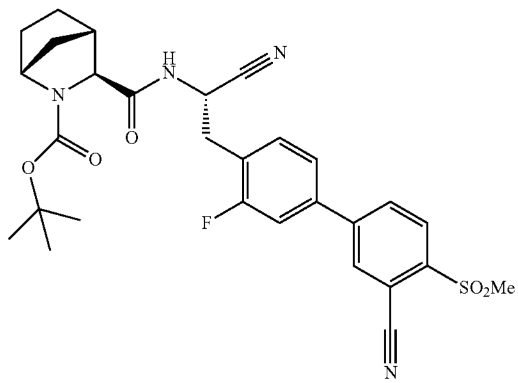
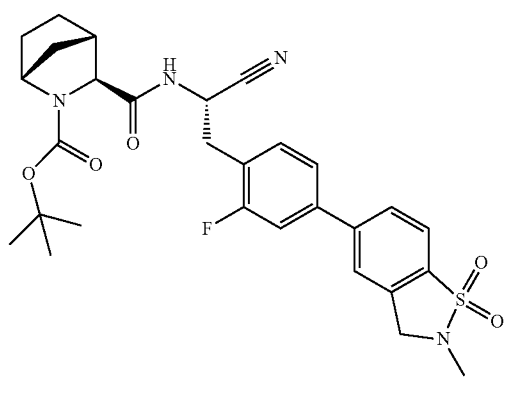
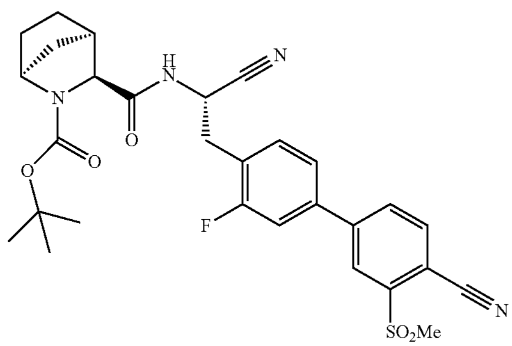
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-1.5.1	I-1.4.1		567	1.24	V018_S01
I-1.5.2	I-1.4.2		569	1.24	V011_S01

TABLE 5-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-1.5.3	I-1.4.3		567	1.14	V011_S01

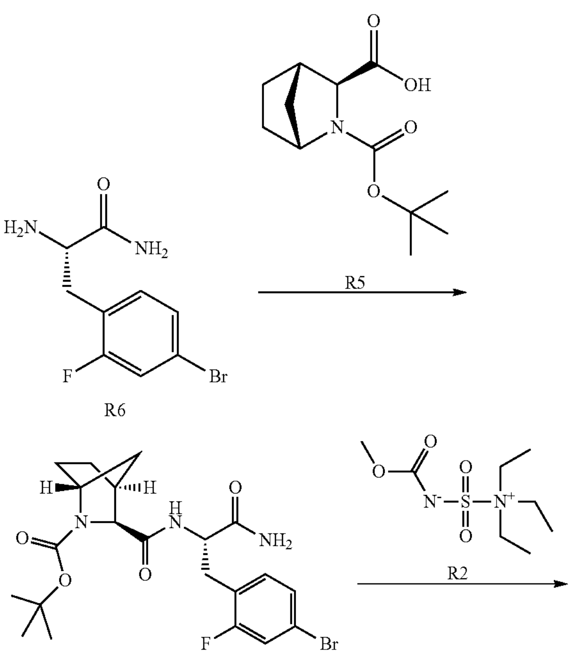
Step 6: Synthesis of Example 1

To I-1.5 (120 mg, 0.23 mmol) in acetonitrile, p-toluenesulfonic acid monohydrate (110 mg, 0.58 mmol) is added and stirred for 3 d. The reaction solution is purified by reversed phase HPLC. Yield 47%, m/z 419 [M+H]+, rt 1.16 min, LC-MS Method V011_S01.

Method A1

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-(1-methyl-2-oxo-indolin-6-yl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

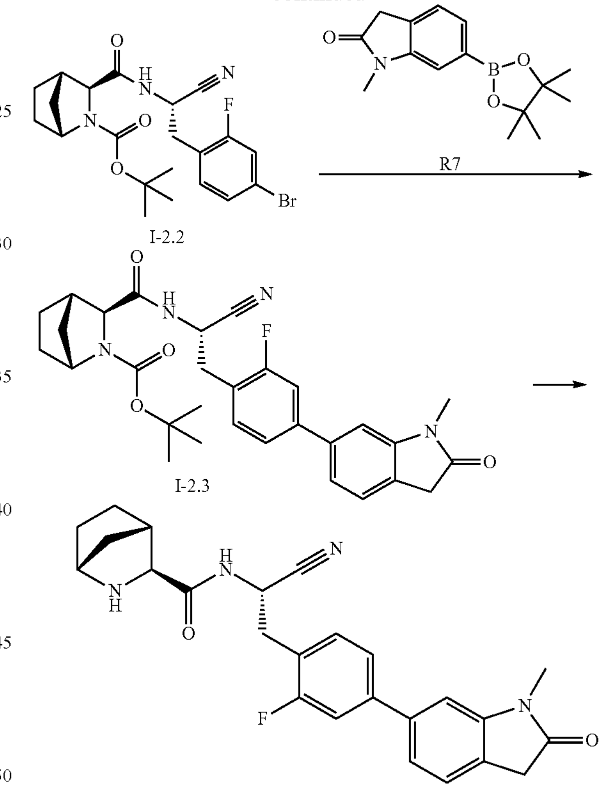
Example 2



R6

I-2.1

-continued



I-2.2

I-2.3

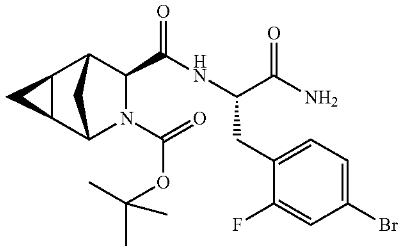
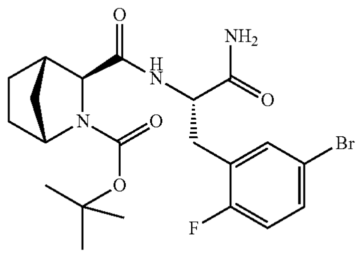
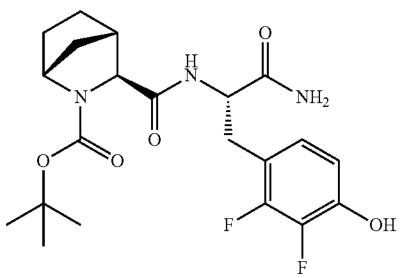
Example 2

Step 1: Synthesis of Intermediate I-2.1

To R5 (7.59 g, 31 mmol) in DCM (300 mL) diisopropylethylamine (4.8 mL, 28 mmol) and HATU (11.5 g, 30 mmol) are added and stirred for 25 min. Then R6 (10.4 g, 28 mmol) and diisopropylethylamine (7.2 mL, 42 mmol) are added and stirred for 3 h. The solvent is evaporated, dissolved in ethyl acetate and washed with water, 0.5 M HCl and aq. NaHCO3 solution (10%). The organic layer is dried over $MgSO_4$, filtrated and concentrated. The residue is purified by flash chromatography (using solvent mixture DCM/methanol=95/5). Yield >95%, m/z 484 [M+H]+, rt 1.18 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 6 are synthesized in a similar fashion from the appropriate intermediate:

TABLE 6

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-2.1.1		496	0.95	Z018_S04
I-2.1.2		484/486	0.71	X018_S02
I-2.1.3		440	0.55	Z011_S03

Step 2: Synthesis of Intermediate I-2.2

To I-2.1 (12.7 g, 26 mmol) in DCM (130 mL) R2 (12.5 g, 52 mmol) is added. The reaction mixture is stirred for 12 h. The solvent is evaporated, dissolved in ethyl acetate and washed with water, 0.1 M HCl and aq. NaHCO3 solution (5%). The organic layer is dried over $MgSO_4$ and concentrated. The residue is recrystallized from DCM and acetonitrile. Yield 64% m/z 466 [M+H]+, rt 1.30 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 7 are synthesized in a similar fashion from the appropriate intermediate:

TABLE 7

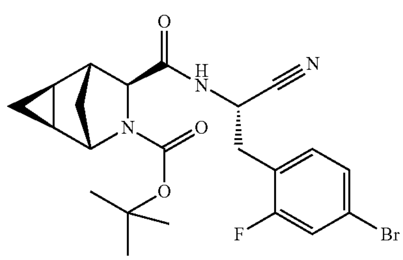
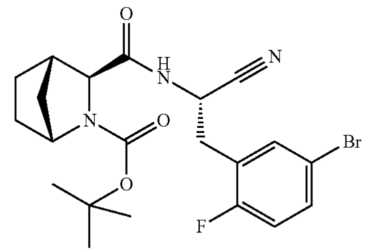
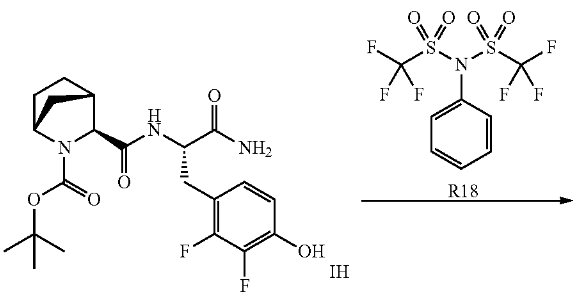
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.2.1	I-2.1.1		478	1.03	Z018_S04

TABLE 7-continued

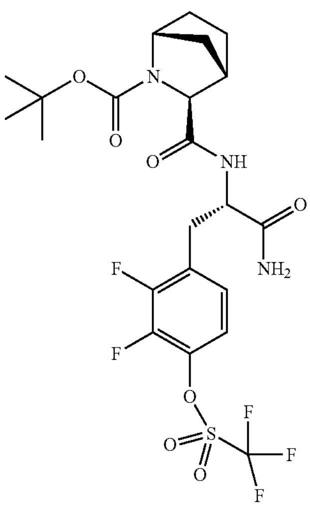
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.2.3	I-2.1.2		466/468	1.27	V011_S01

Synthesis of Intermediate I-2.2.2

Synthesis of tert-butyl (1S,2S,4R)-2-[[(1S)-2-amino-1-[[2,3-difluoro-4-trifluoromethylsulfonyl oxy)phenyl]methyl]-2-oxo-ethyl]carbamoyl]-3-azabicyclo [2.2.1]heptane-3-carboxylate



I-2.1.3



1-2.2.2

The phenol I-2.1.3 is transformed into the corresponding trifluoromethanesulfonate I-2.2.2: I.2.1.3 (200 mg, 0.46 mmol) is dissolved in anhydrous DCM (1.5 mL). Triethylamine (95 μL, 0.69 mmol) is added and the reaction mixture is cooled to 0° C. R18 (179 mg, 0.50 mmol) is then added and the mixture was stirred at 0° C. for 90 minutes and additional 12 h at room temperature. The mixture is concentrated and the residue is purified by reversed phase HPLC. Yield 85%, m/z 472 [M+H−BOC]+, rt 0.97 min, LC-MS Method Z011_S03.

Step 3: Synthesis of Intermediate I-2.3

To I-2.2 (5.00 g, 10 mmol) in acetonitrile (100 mL) R7 (3.07 g, 11 mmol) is added. The mixture is purged with argon, 1,1-Bis(di-tert-butylphosphino)ferrocene palladium dichloride (0.70 g, 1.1 mmol) and aq. sodium carbonate solution (2 mol/L, 1.07 mL) are added and the mixture is heated to 70° C. for 3.5 h. Ethyl acetate and water are added to the reaction mixture. The organic layer is washed with aq. NaHCO3 solution (5%) and water. The organic layer is dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (cyclohexane/ethyl acetate=1/1). Yield 41% m/z 533 [M+H]+, rt 1.25 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 8 are synthesized in a similar fashion from the appropriate intermediates ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 8

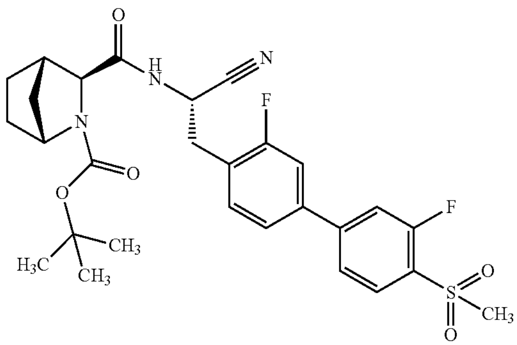
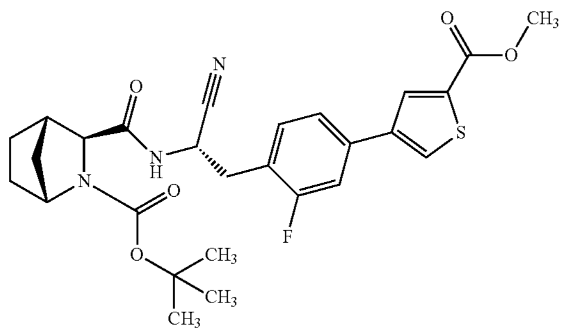
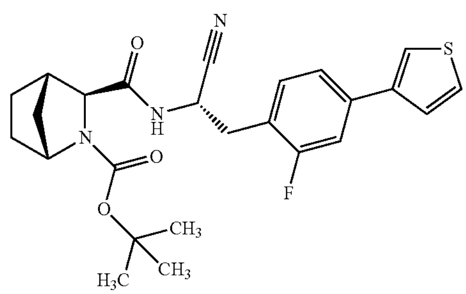
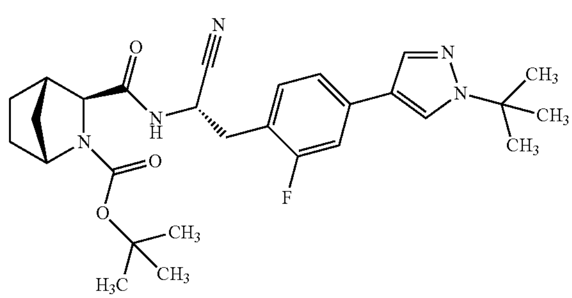
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.1	I-2.2		560	0.76	X018_S01
I-2.3.2	I-2.2		528	0.88	004_CA01
I-2.3.3	I-2.2		470	0.90	004_CA05
I-2.3.4	I-2.2		510	0.87	004_CA05

TABLE 8-continued

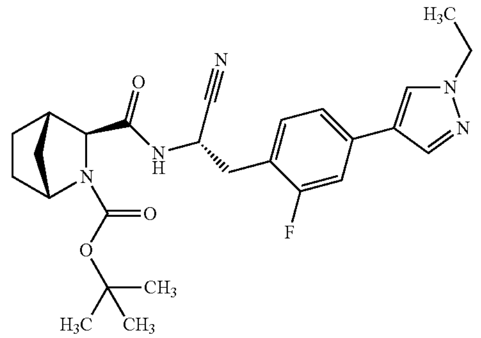
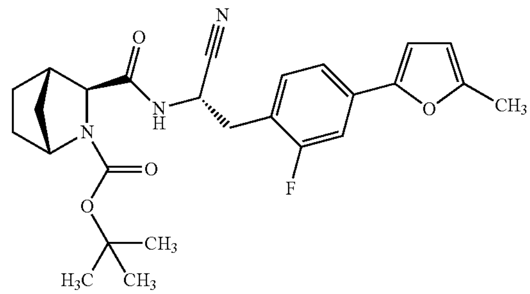
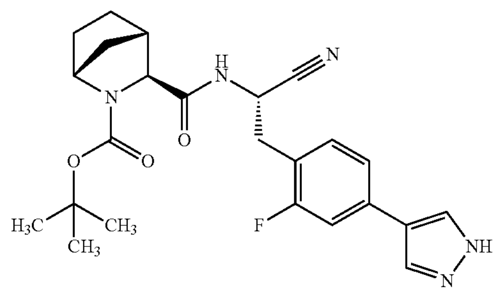
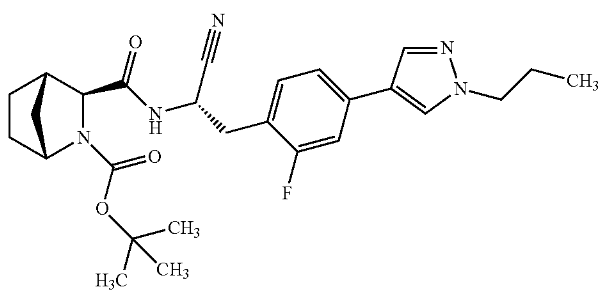
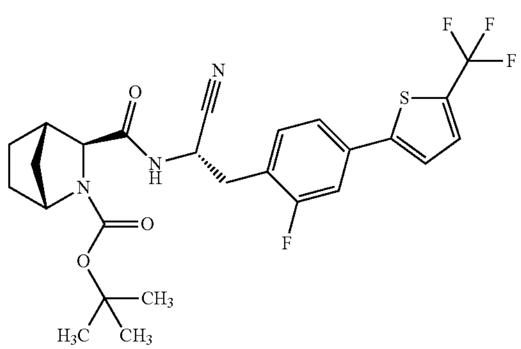
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.5	I-2.2		482	0.77	004_CA05
I-2.3.6	I-2.2		468	0.92	004_CA05
I-2.3.7	I-2.2		454	0.82	Z011_S03
I-2.3.8	I-2.2		496	0.82	004_CA05
I-2.3.9	I-2.2		538	1.00	004_CA05

TABLE 8-continued

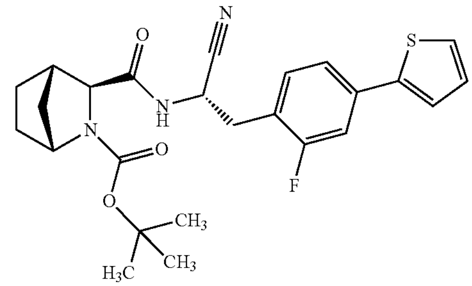
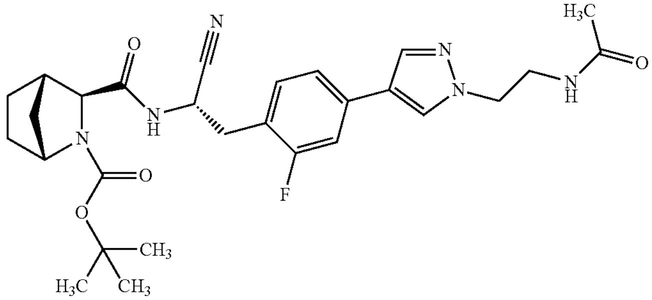
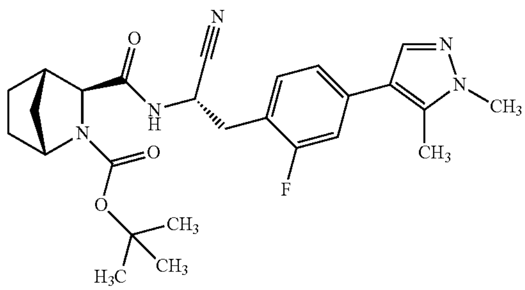
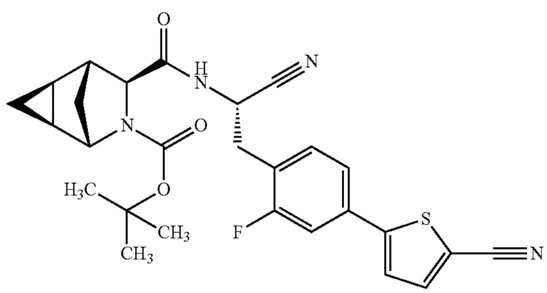
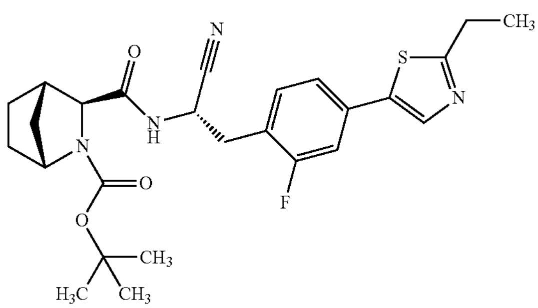
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.10	I-2.2		470	0.91	004_CA05
I-2.3.11	I-2.2		539	0.66	004_CA05
I-2.3.12	I-2.2		482	0.75	004_CA05
I-2.3.13	I-2.2.1		407	1.03	Z018_S04
I-2.3.14	I-2.2		499	0.86	004_CA05

TABLE 8-continued

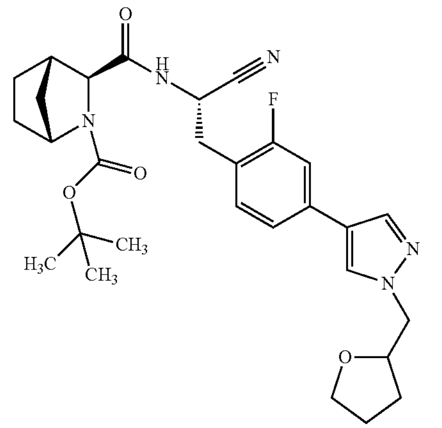
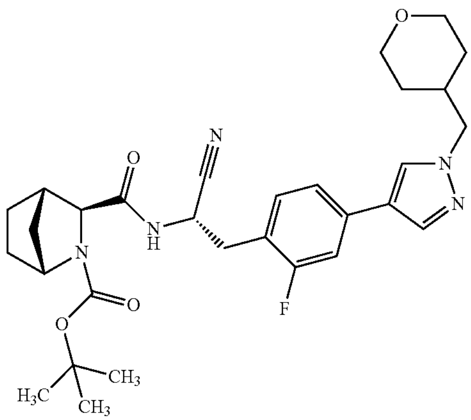
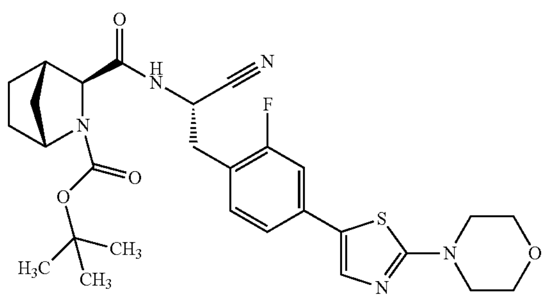
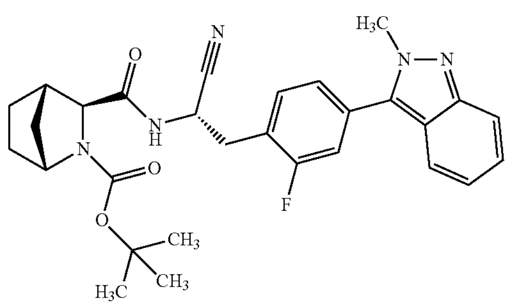
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.15	I-2.2		438 [M + H − BOC]+	0.94	X018_S04
I-2.3.16	I-2.2		552	0.77	004_CA05
I-2.3.17	I-2.2		556	0.91	X018_S04
I-2.3.18	I-2.2		518	0.89	004_CA05

TABLE 8-continued

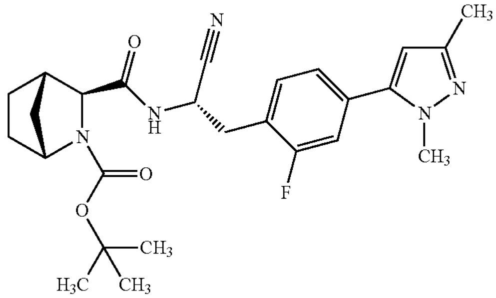
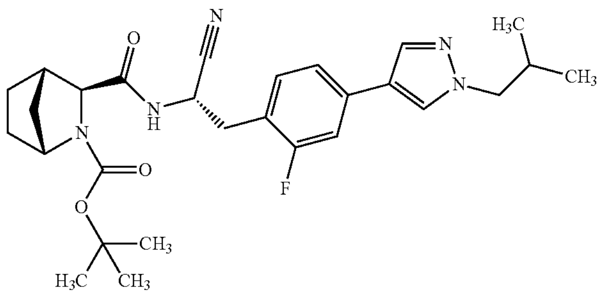
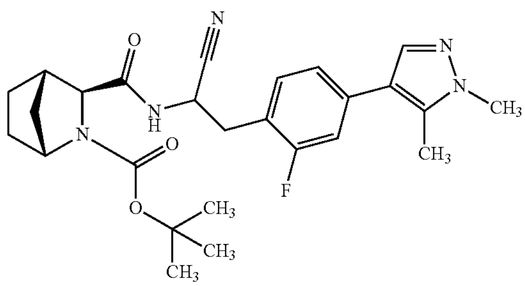
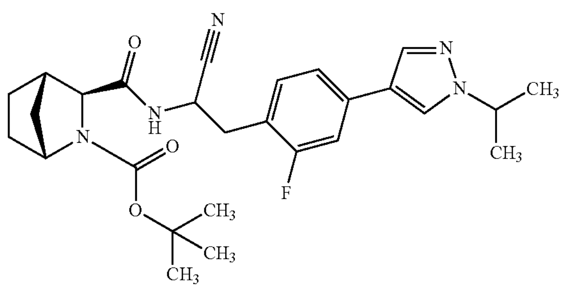
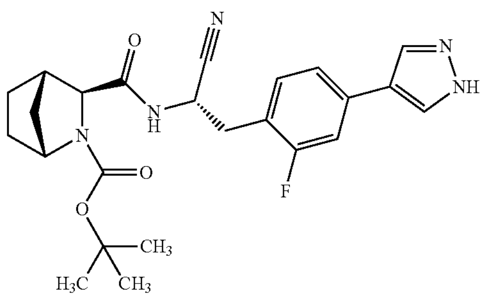
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.19	I-2.2		482	0.77	004_CA05
I-2.3.20	I-2.2		510	0.86	004_CA05
I-2.3.21	I-2.2		482	0.75	004_CA01
I-2.3.22	I-2.2		496	0.82	004_CA01
I-2.3.23	I-2.2		554	0.68	004_CA05

TABLE 8-continued

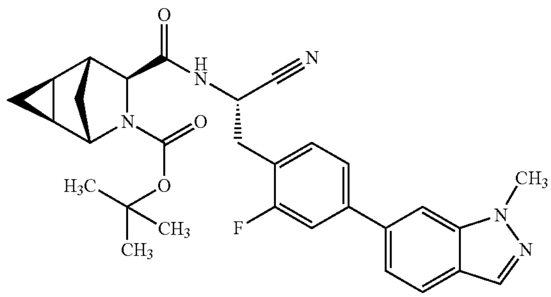
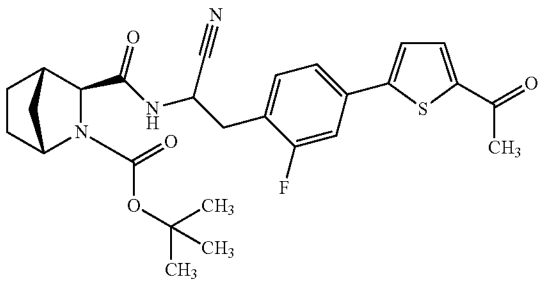
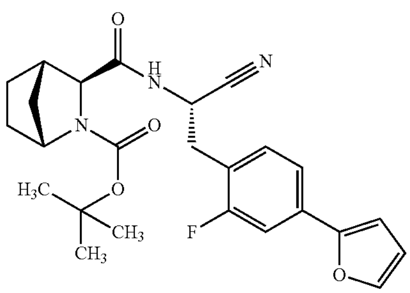
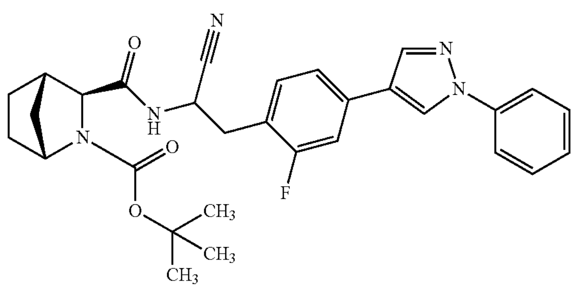
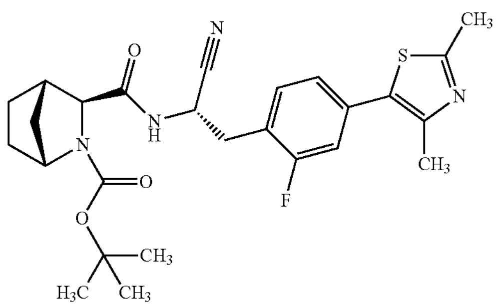
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.24	I-2.2.1		530	1.02	Z018_S04
I-2.3.25	I-2.2		512	0.83	004_CA01
I-2.3.26	I-2.2		354	1.02	Z018_S04
I-2.3.27	I-2.2		530	0.91	004_CA01
I-2.3.28	I-2.2		499	0.82	004_CA05

TABLE 8-continued

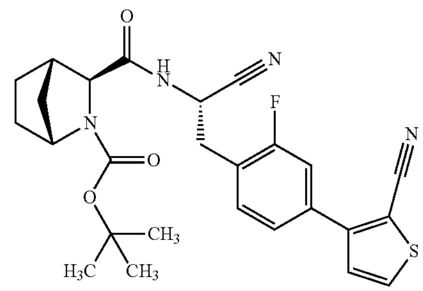
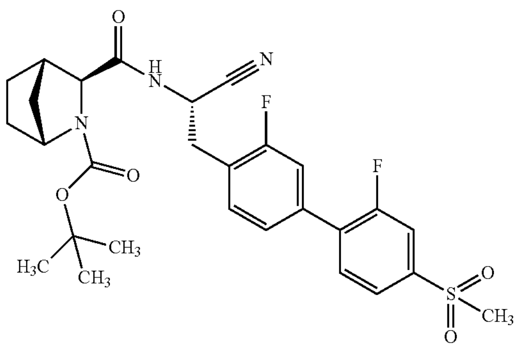
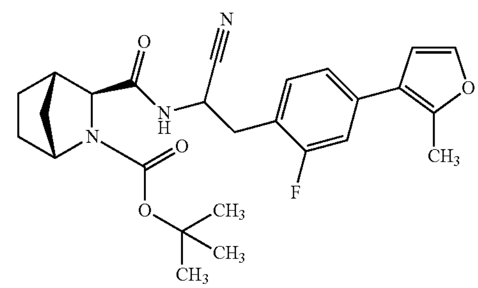
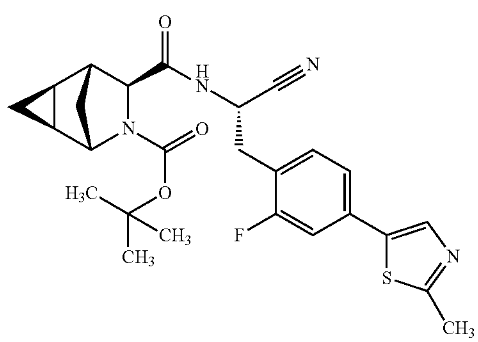
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.29	I-2.2		395 [M + H − BOC]+	1.02	Z018_S04
I-2.3.30	I-2.2		560	0.76	X018_S01
I-2.3.31	I-2.2		468	0.9	004_CA01
I-2.3.32	I-2.2.1		397	0.97	Z018_S04

TABLE 8-continued

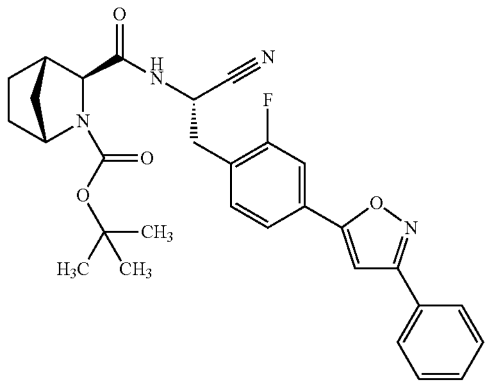
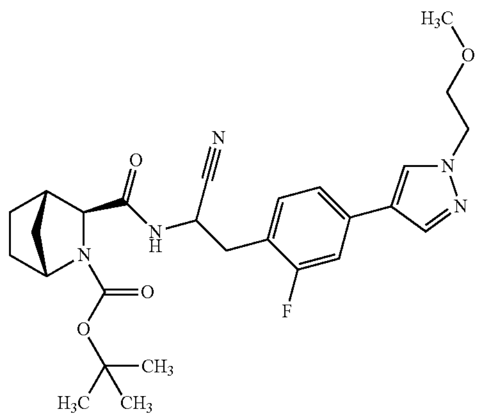
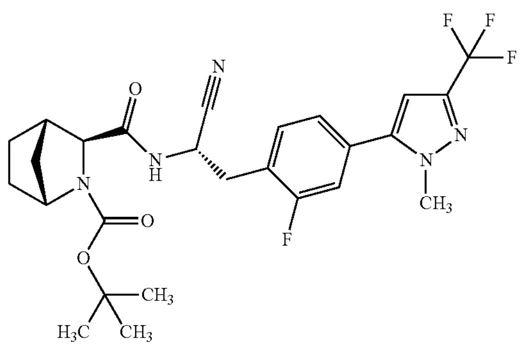
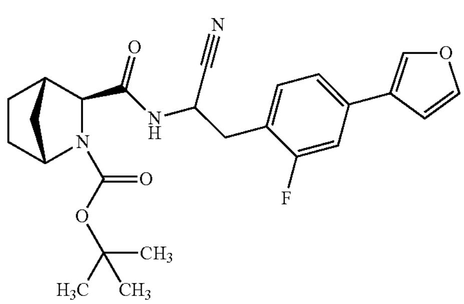
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.33	I-2.2		431	1.07	Z018_S04
I-2.3.34	I-2.2		512	0.75	004_CA01
I-2.3.35	I-2.2		536	0.89	004_CA05
I-2.3.36	I-2.2		454	0.85	004_CA01

TABLE 8-continued

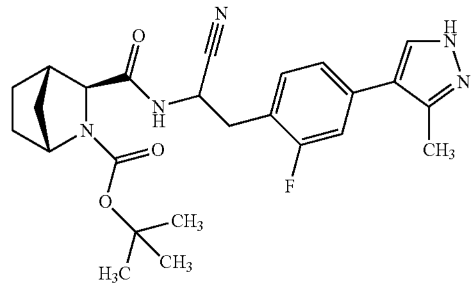
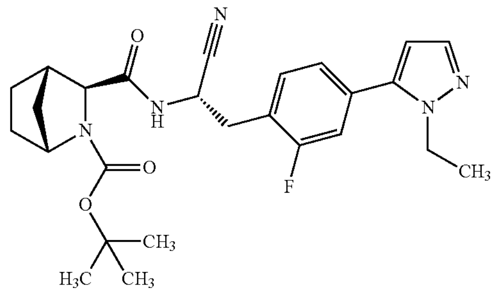
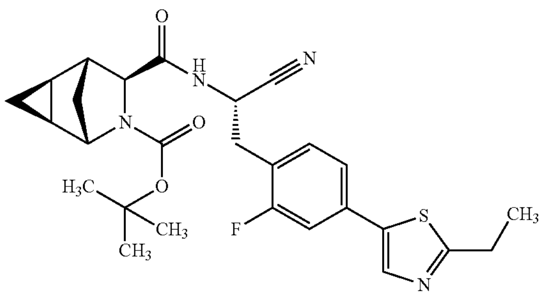
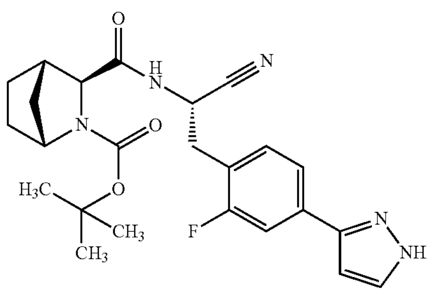
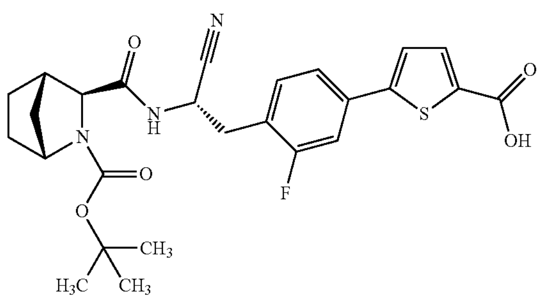
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.37	I-2.2		468	0.69	004_CA01
I-2.3.38	I-2.2		482	0.78	004_CA01
I-2.3.39	I-2.2.1		411	1.01	Z018_S04
I-2.3.40	I-2.2		354	0.87	Z018_S04
I-2.3.41	I-2.2		514	0.44	004_CA05

TABLE 8-continued

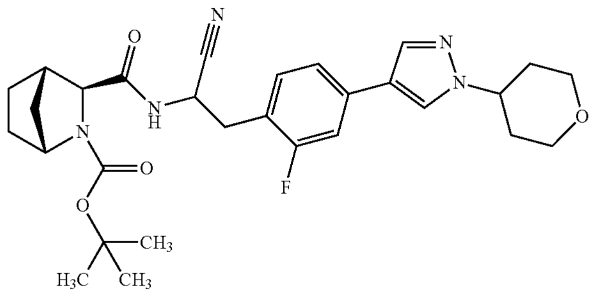
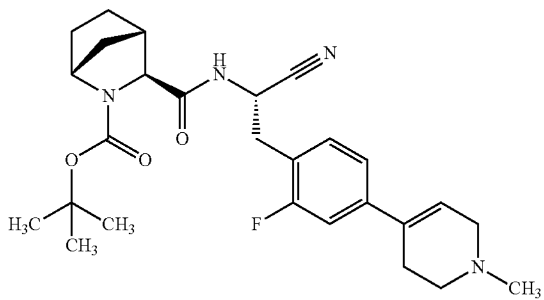
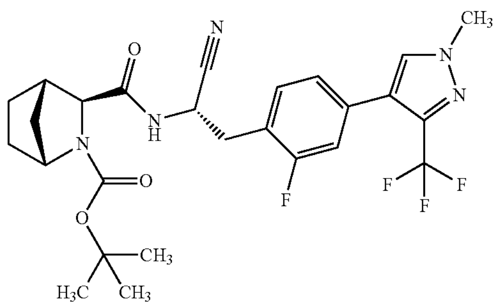
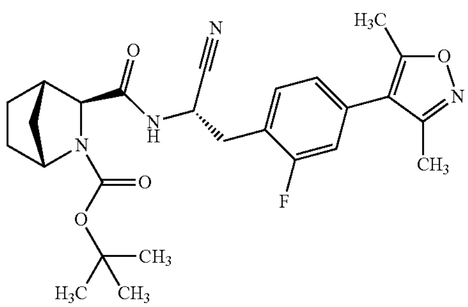
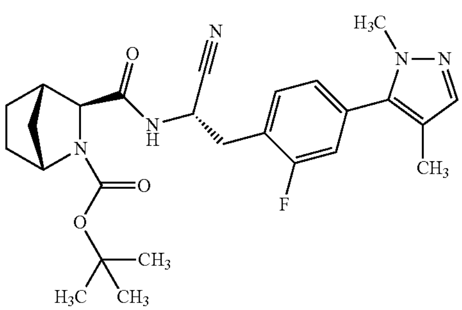
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.42	I-2.2		538	0.76	004_CA01
I-2.3.43	I-2.2		483	0.93	V012_S01
I-2.3.44	I-2.2		536	0.85	004_CA05
I-2.3.45	I-2.2		483	0.81	004_CA05
I-2.3.46	I-2.2		482	0.77	004_CA05

TABLE 8-continued

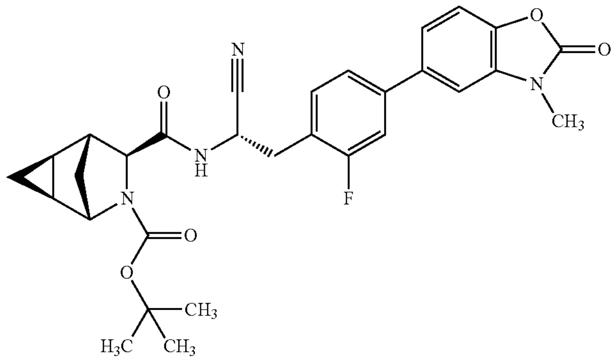
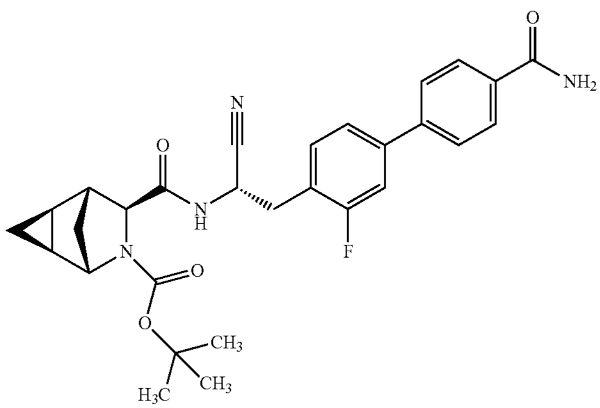
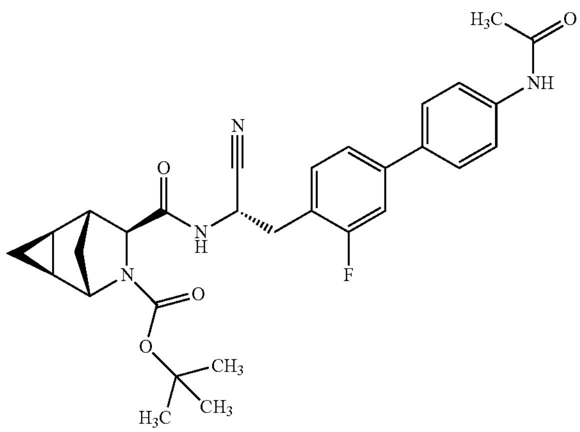
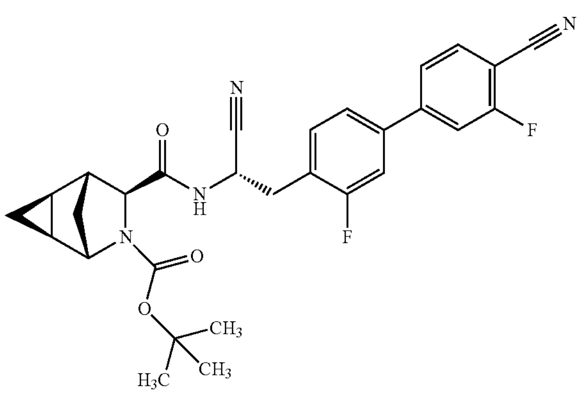
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.47	I-2.2.1		547	0.83	004_CA05
I-2.3.48	I-2.2.1		519	0.71	004_CA05
I-2.3.49	I-2.2.1		533	0.77	004_CA05
I-2.3.50	I-2.2.1		519	0.89	004_CA05

TABLE 8-continued

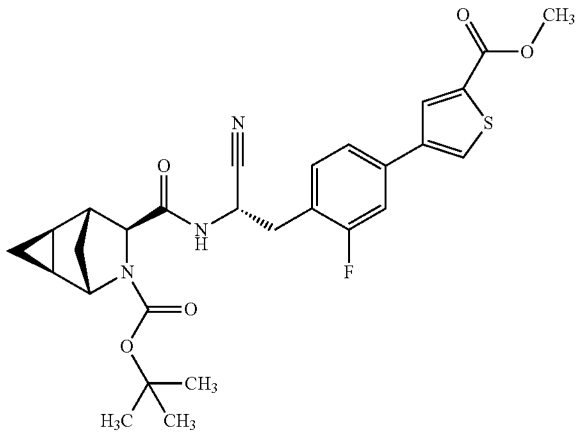
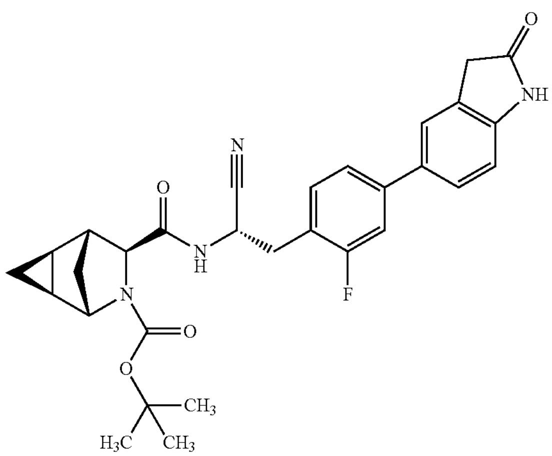
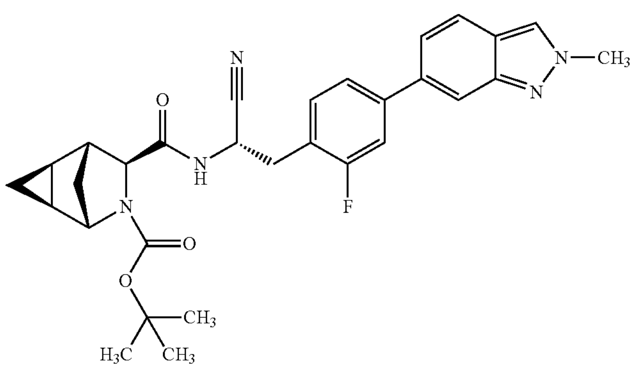
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.51	I-2.2.1		540	0.9	004_CA05
I-2.3.52	I-2.2.1		531	0.74	004_CA05
I-2.3.53	I-2.2.1		530	0.81	004_CA05

TABLE 8-continued

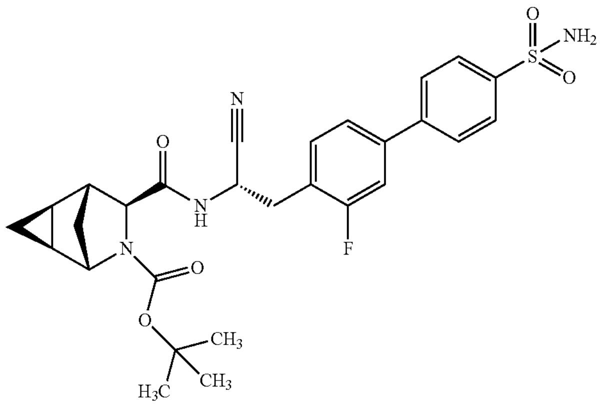
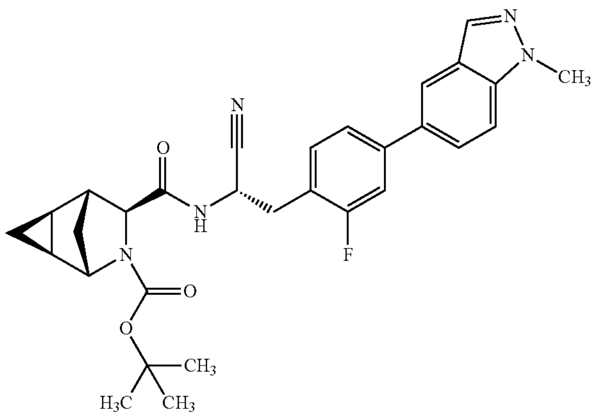
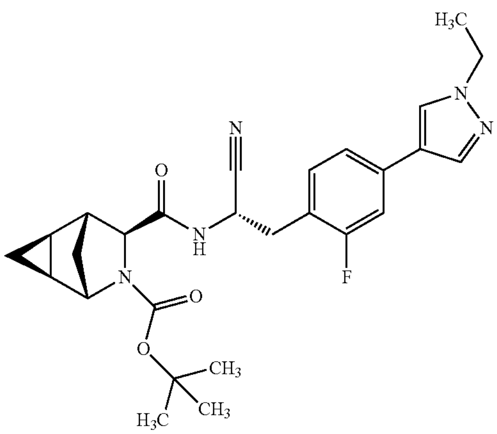
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.54	I-2.2.1		555	0.72	004_CA05
I-2.3.55	I-2.2.1		530	0.85	004_CA05
I-2.3.56	I-2.2.1		494	0.79	004_CA05

TABLE 8-continued

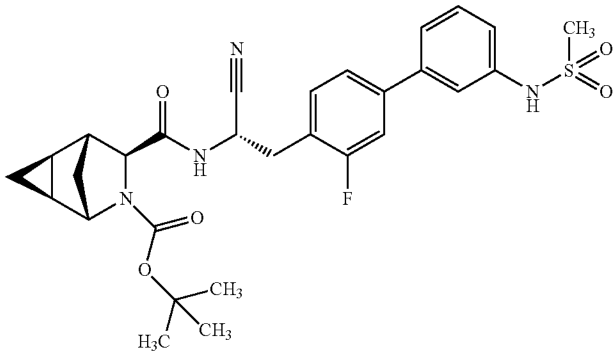
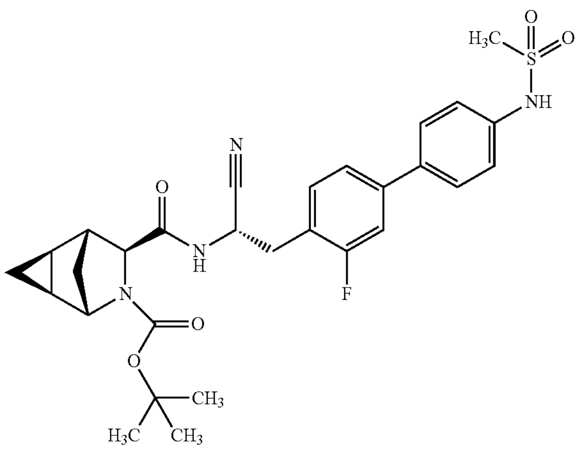
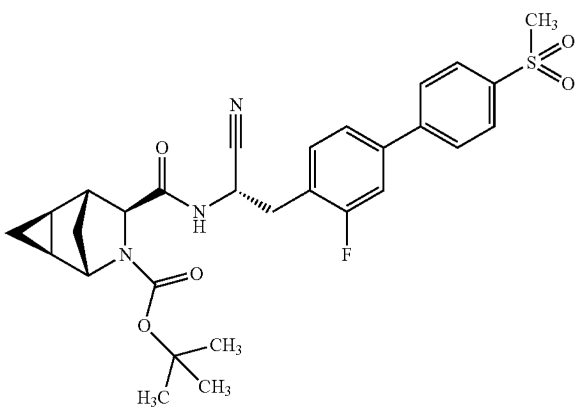
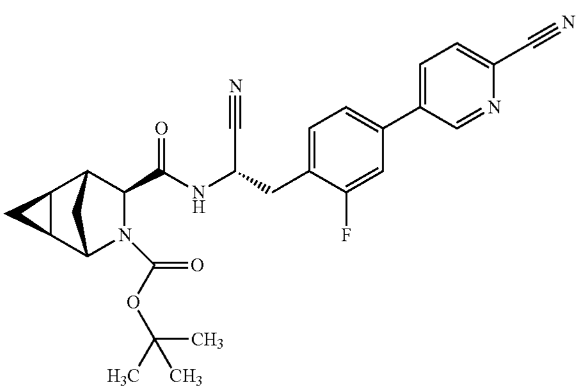
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.57	I-2.2.1		569	0.71	004_CA05
I-2.3.58	I-2.2.1		569	0.66	004_CA05
I-2.3.59	I-2.2.1		554	0.79	004_CA05
I-2.3.60	I-2.2.1		502	0.81	004_CA05

TABLE 8-continued

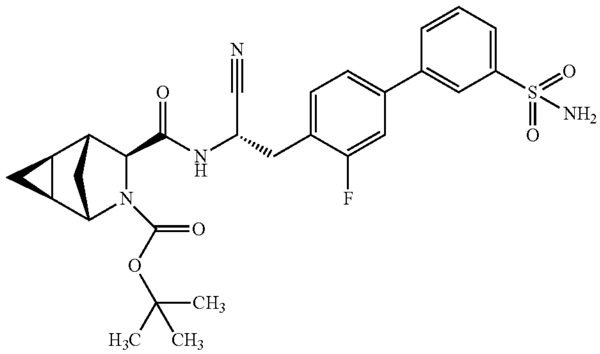
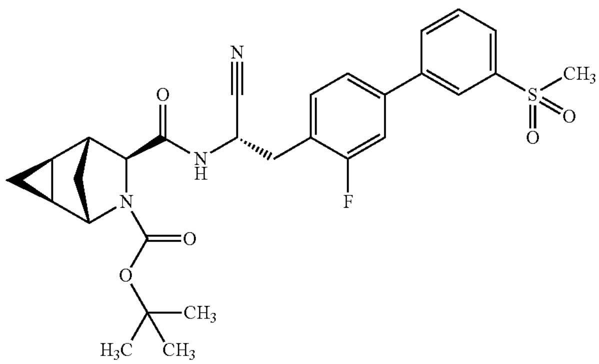
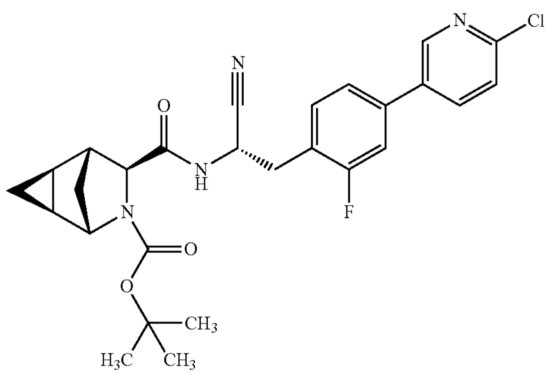
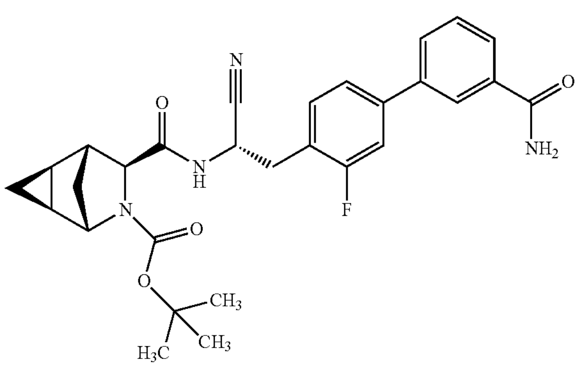
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.61	I-2.2.1		555	0.74	004_CA05
I-2.3.62	I-2.2.1		554	0.79	004_CA05
I-2.3.63	I-2.2.1		511	0.87	004_CA05
I-2.3.64	I-2.2.1		519	0.73	004_CA05

TABLE 8-continued

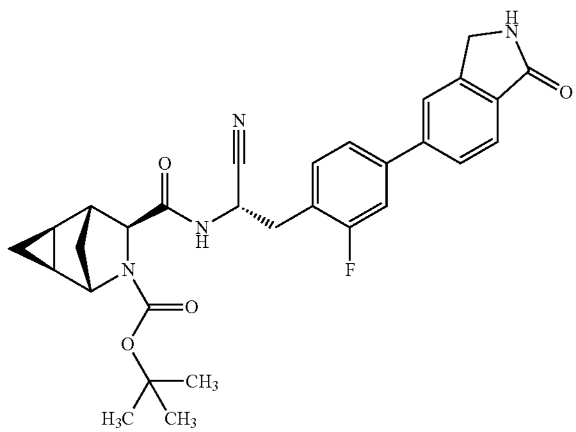
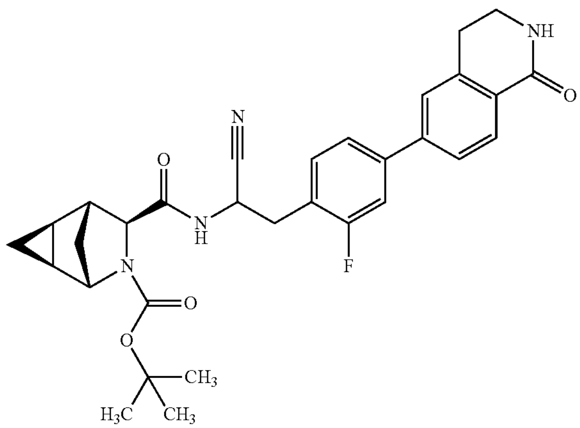
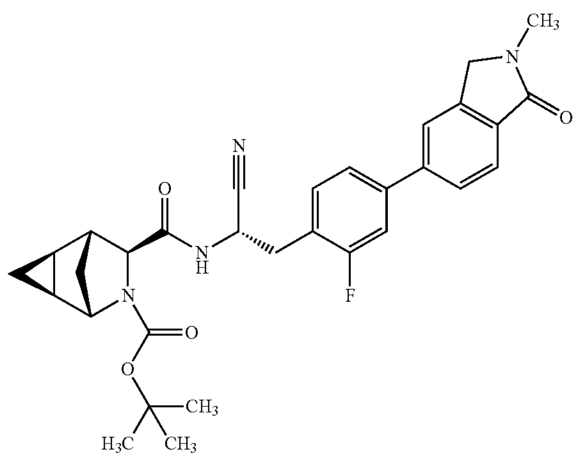
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.65	I-2.2.1		531	0.71	004_CA05
I-2.3.66	I-2.2.1		545	0.74	004_CA05
I-2.3.67	I-2.2.1		545	0.76	004_CA05

TABLE 8-continued

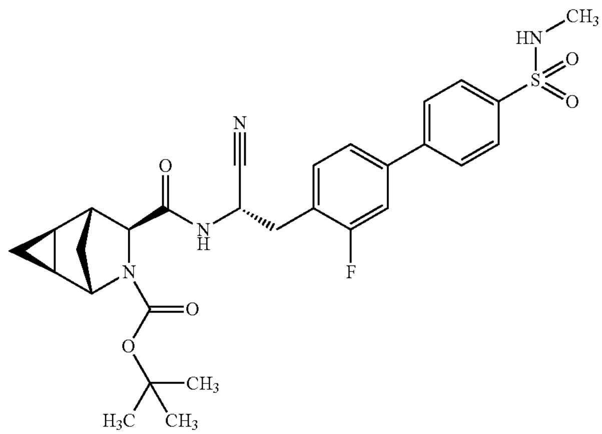
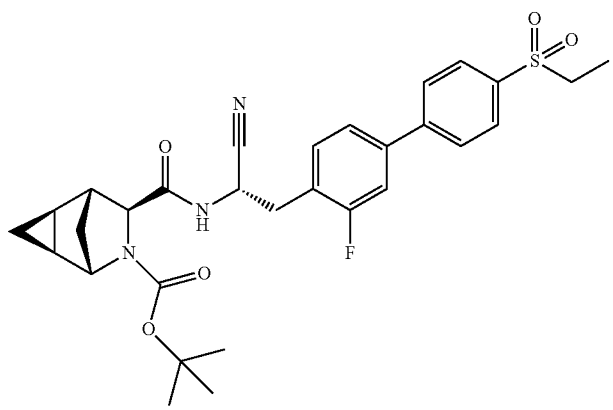
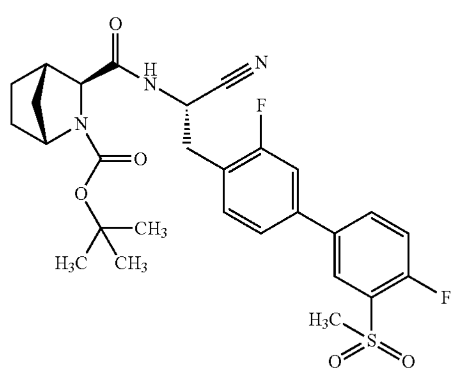
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.68	I-2.2.1		569	0.79	004_CA05
I-2.3.69	I-2.2.1		568	0.82	004_CA05
I-2.3.70	I-2.2		460 [M + H − BOC]+	0.97	X018_S04

TABLE 8-continued

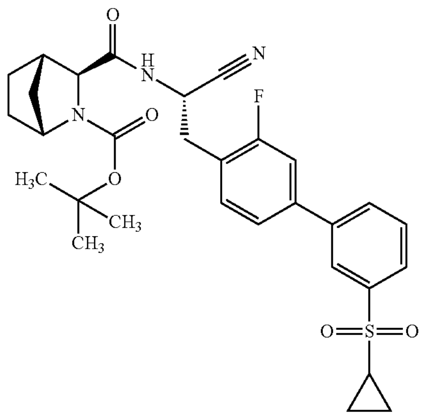
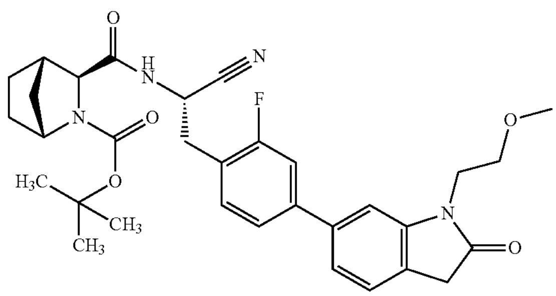
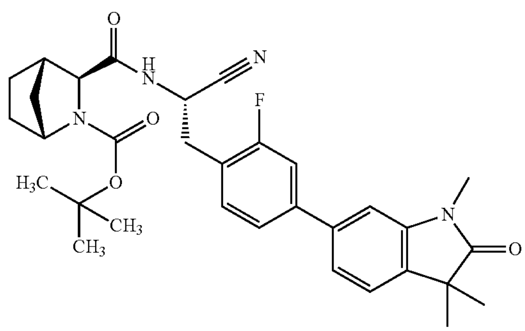
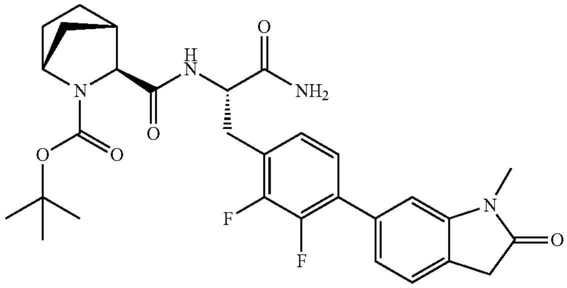
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.71	I-2.2		468 [M + H − BOC]+	1.00	X018_S04
I-2.3.72	I-2.2		577	n.d.	n.d.
I-2.3.73	I-2.2		561	n.d.	n.d.
I-2.3.74	I-2.2.2		469	0.89	Z018_S04

TABLE 8-continued

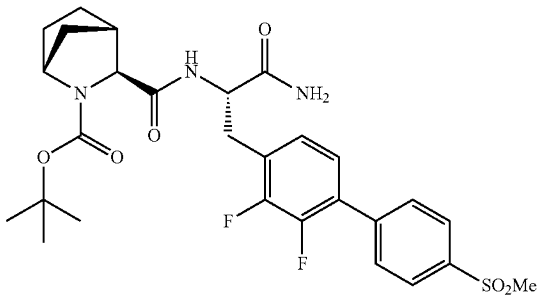
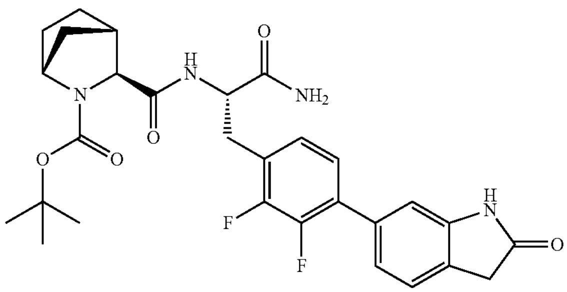
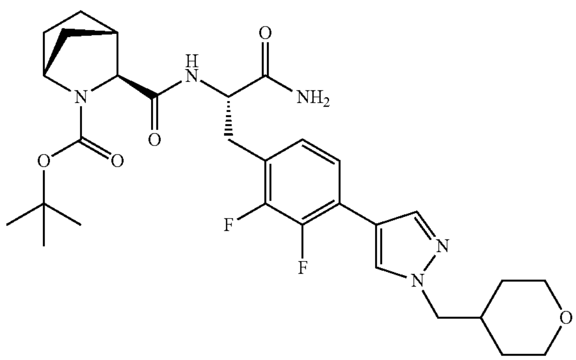
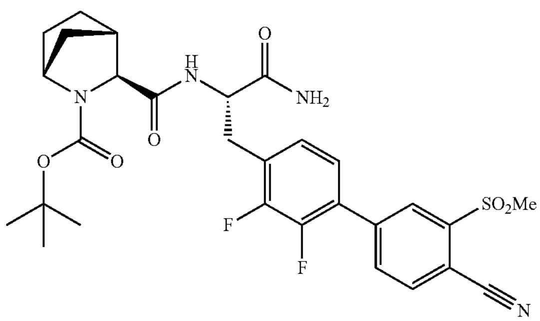
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.75	I-2.2.2		578	0.88	Z018_S04
I-2.3.76	I-2.2.2		455 (M + H − BOC)+	0.85	Z018_S04
I-2.3.77	I-2.2.2		488 (M + H − BOC)	0.89	Z018_S04
I-2.3.78	I-2.2.2		503 (M + H − BOC)+	0.89	Z018_S04

TABLE 8-continued

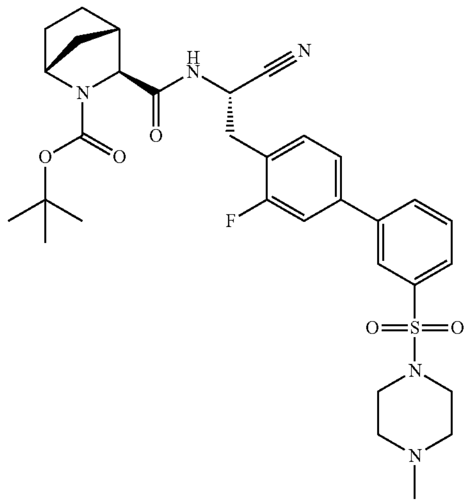
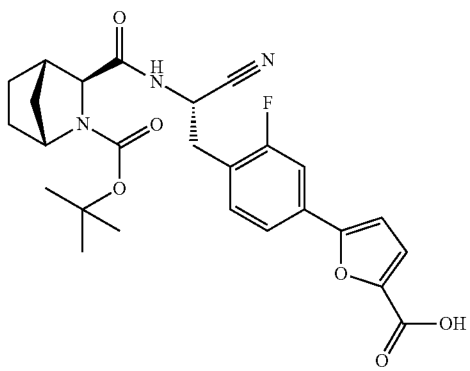
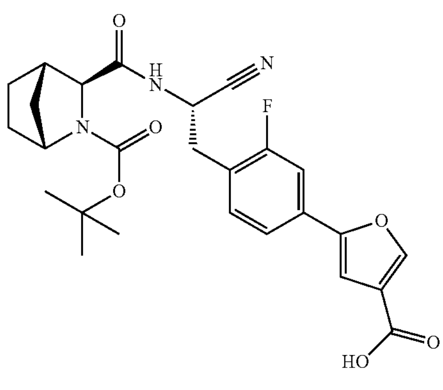
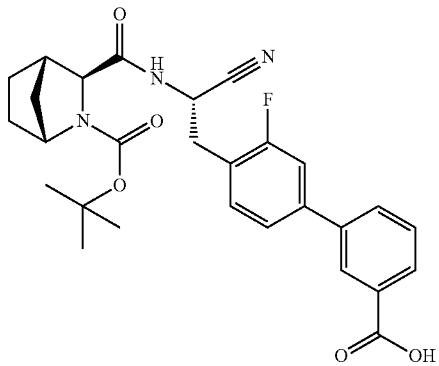
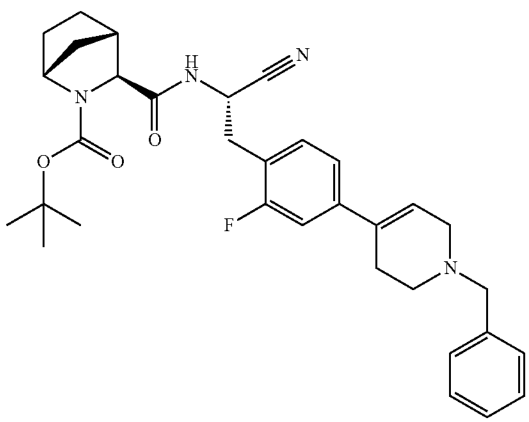
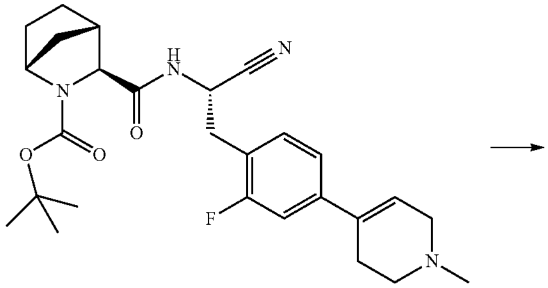
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.79	I-2.2		626	0.54	X012_S01
I-2.3.80	I-2.2		398 (M + H − BOC)+	0.89	Z018_S04
I-2.3.81	I-2.2		398 (M + H − BOC)+	0.89	n.d.

TABLE 8-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.82	I-2.2		508	0.94	Z018_S04
I-2.3.83	I-2.2		n.d.	n.d.	n.d.

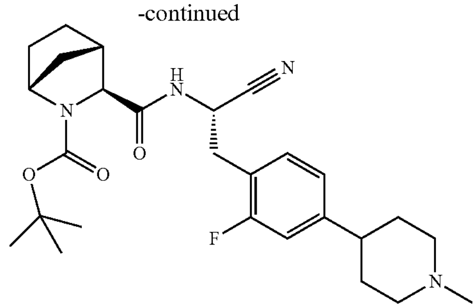
During the synthesis of intermediates I-2.3.17 and I-2.3.29 the bromide (I-2.2) is transformed into the corresponding dioxaborolane compound. Coupling with aromatic bromides is performed in analogy to the synthesis of intermediate I-1.3 (method A).

Intermediate I-2.3.43 is further processed via hydrogenation before the BOC group is removed (step 4)



I-2.3.43

-continued

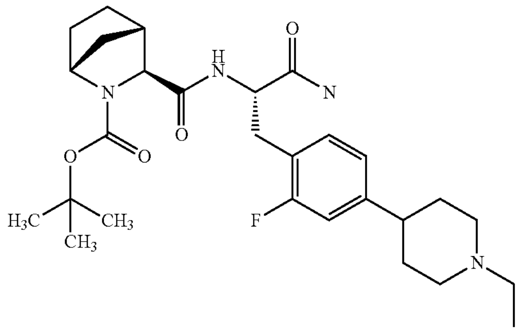
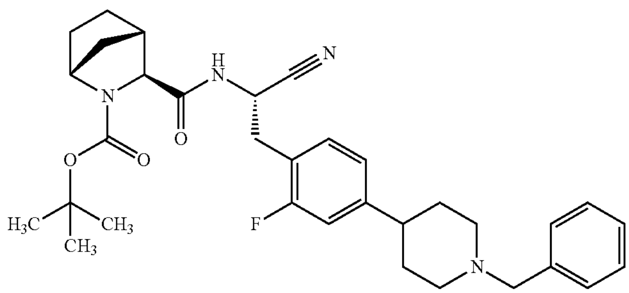


I-2.3.43.1

To I-2.3.43 (90 mg, 0.19 mmol) in methanol (10 mL) Pd/C (10%, 20 mg) is added. The reaction mixture is stirred under hydrogen (50 psi) for 3 h. Then the mixture is filtered and concentrated. The crude product is carried on with step 4. Yield >95%

In analogy the following intermediates as shown in Table 9 are prepared.

TABLE 9

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.43.2	I-3.2.78		517	0.47.	X012_S02
I-2.3.43.3	I-2.3.83		561	n.d.	n.d.

Intermediates I-2.3.74-78 and I-2.3.43.2 are converted to the corresponding nitriles in analogy to step 2 of method A1 to yield the compounds in the following Table 10.

TABLE 10

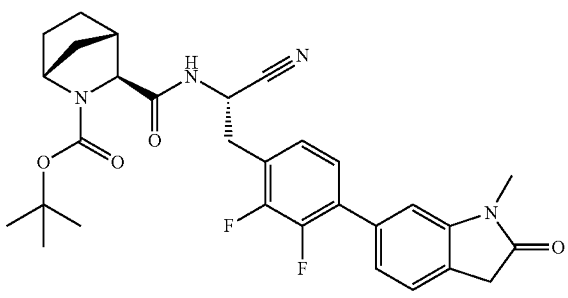
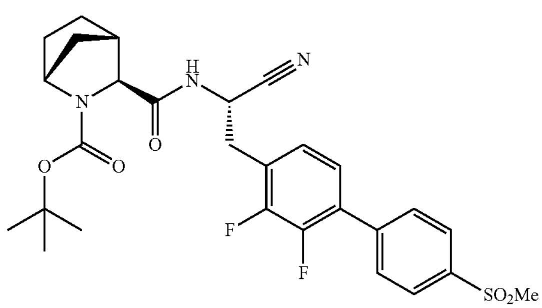
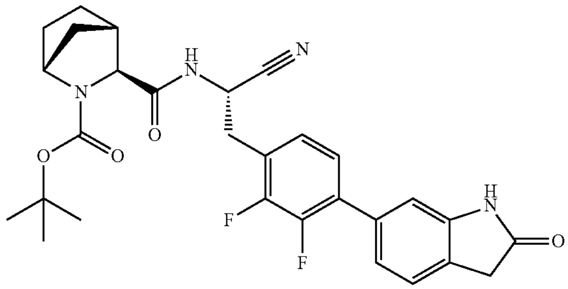
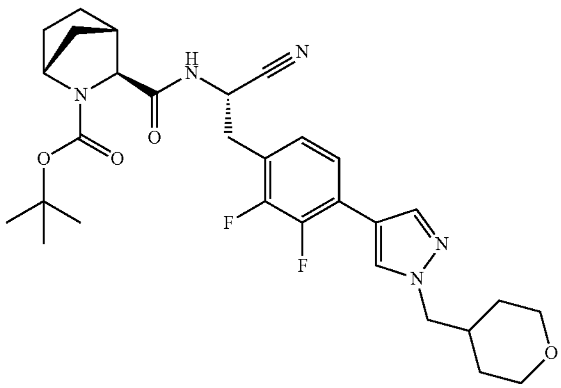
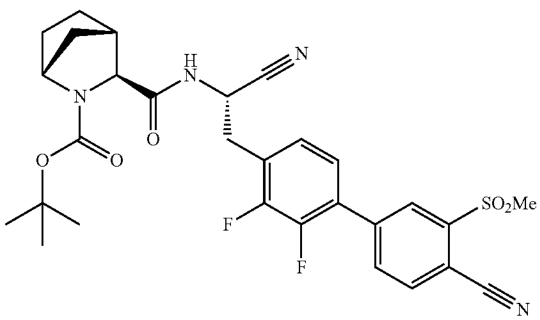
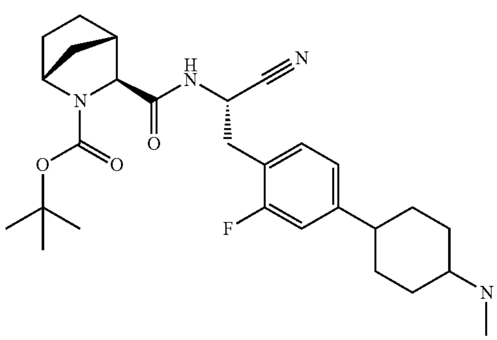
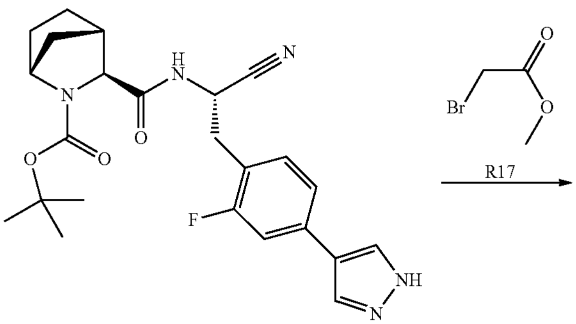
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.74.1	I-2.3.74		451 [M + H − BOC]+	0.98	Z018_S01
I-2.3.75.1	I-2.3.75		460 (M + H+) − BOC	0.96	Z018_S04

TABLE 10-continued

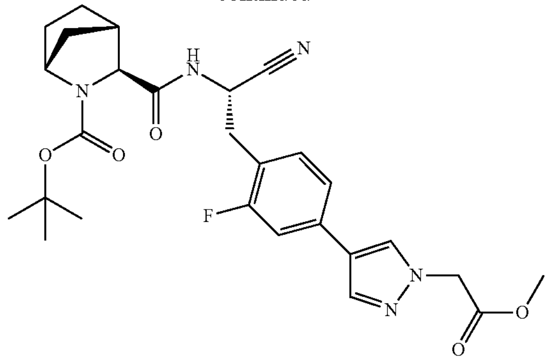
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.76.1	I-2.3.76		437 (M + H − BOC)+	0.93	Z018_S04
I-2.3.77.1	I-2.3.77		470 (M + H − BOC)+	0.96	Z018_S04
I-2.3.78.1	I-2.3.78		485 (M + H − BOC)+	0.96	Z018_S04
I-2.3.43.1	I-2.3.43.2		499	0.54	Z018_S02

The intermediate I-2.3.7 is combined with appropriate halogenides or acid chlorides before (in step 4) the BOC group is removed



I-2.3.7

-continued



I-2.3.7.1

To I-2.3.7 (45 mg, 0.10 mmol) and R17 (19 μL, 0.20 mmol) in DMF (1.5 mL) potassium carbonate (42 mg, 0.30 mmol) is added. The reaction mixture is heated to 80° C. for 12 h. The mixture is purified directly by reversed phase HPLC. Yield 65%, m/z 526 [M+H]+, rt 0.71 min, LC-MS Method X018_S01.

The following intermediates as shown in Table 11 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 11

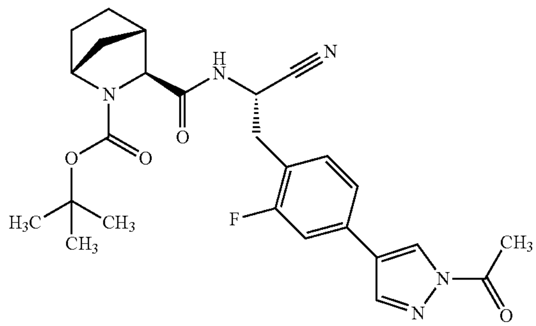
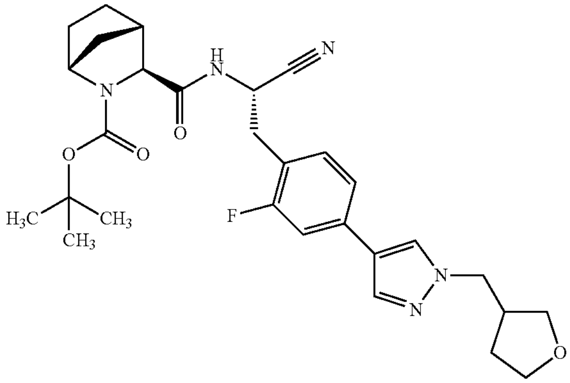
Intermediate	educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.7.3	I-2.3.7		496	0.77	X018_S01
I-2.3.7.4	I-2.3.7		538	0.72	X018_S01

TABLE 11-continued

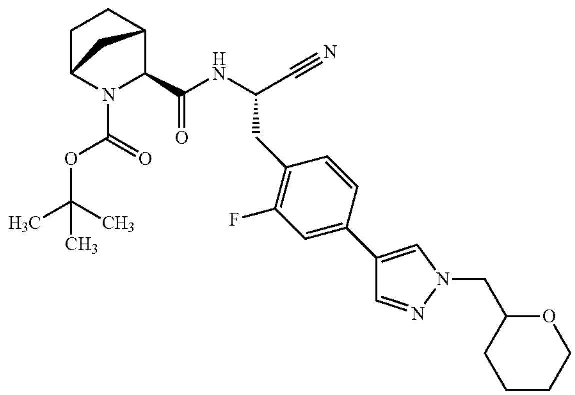
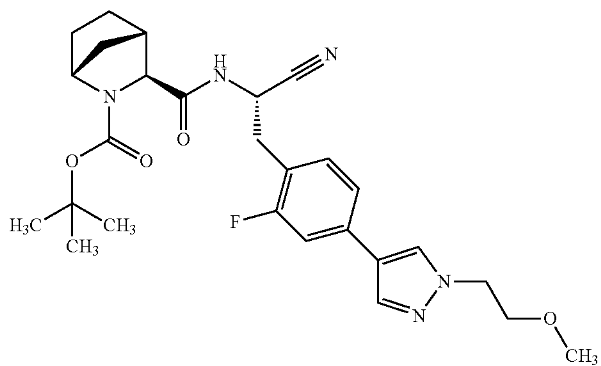
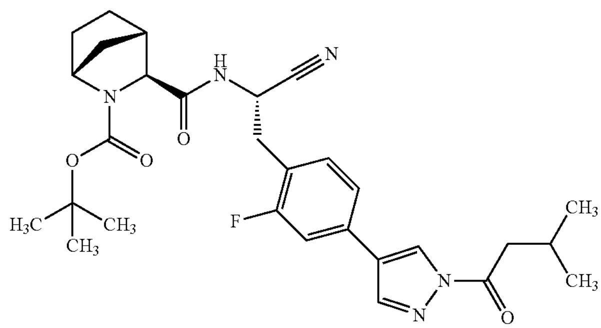
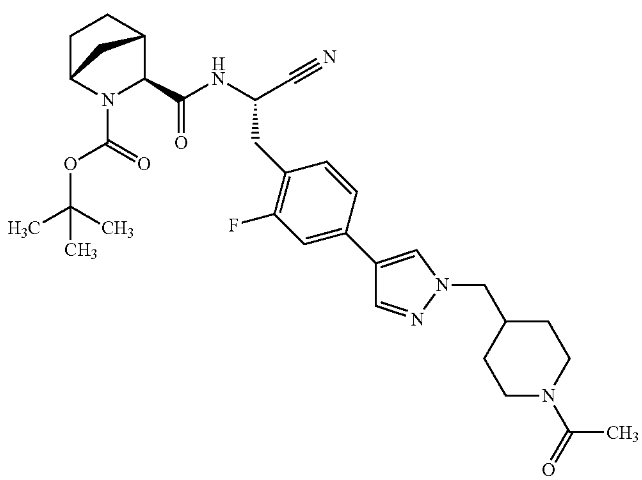
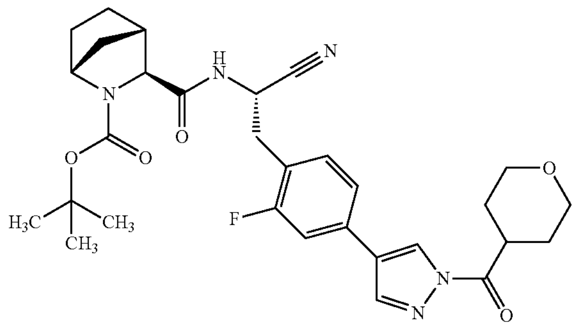
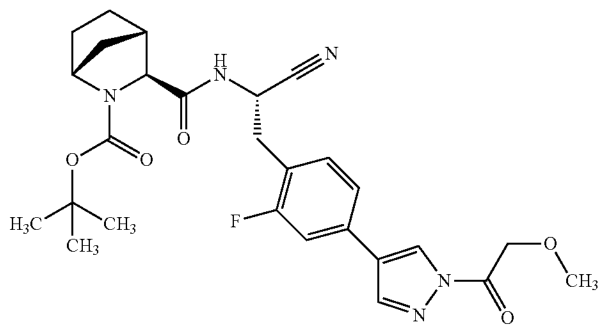
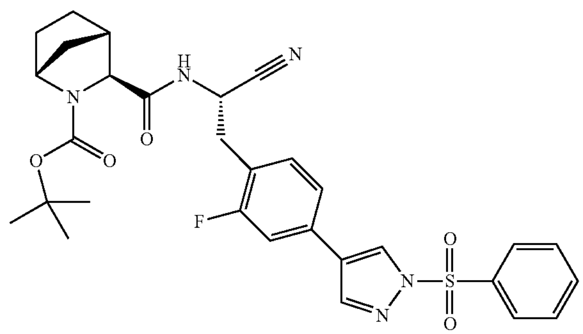
Intermediate	educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.7.5	I-2.3.7		552	0.79	X018_S01
I-2.3.7.6	I-2.3.7		512	0.72	X018_S01
I-2.3.7.7	I-2.3.7		438 [M + H − BOC]+	1.11	X018_S01
I-2.3.7.8	I-2.3.7		593	0.69	X018_S01

TABLE 11-continued

Intermediate	educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.7.9	I-2.3.7		566	0.79	X018_S01
I-2.3.7.10	I-2.3.7		526	0.75	X018_S01
I-2.3.7.11	I-2.3.7		494 (M + H − BOC)+	1.03	Z018_S04

The reaction conditions for I-2.3.7.11 differ: Pyridine and dichlormethane instead of potassium carbonate and DMF is used.

Intermediate I-2.3.7.4 is separated according to method chiral SFC B to give the following intermediates as shown in Table 11.1

TABLE 11.1

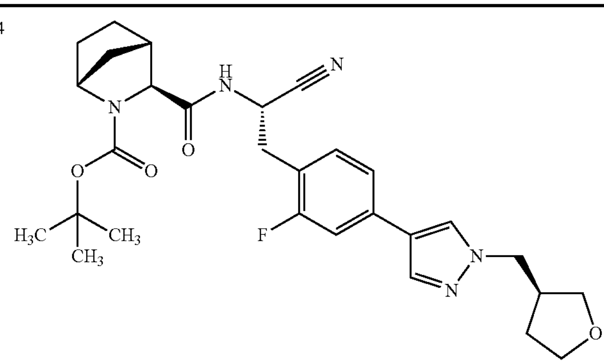
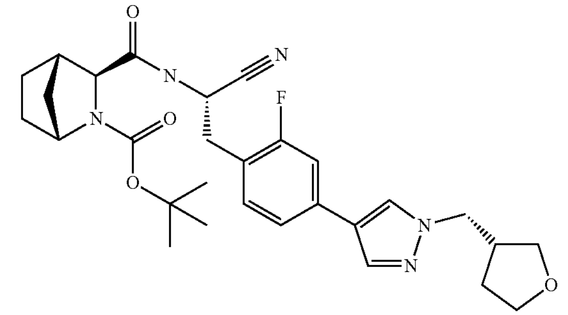
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.7.4.1	I-2.3.7.4		n.d.	3.90	I_OJH_10_IPROP_DEA.M

TABLE 11.1-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-2.3.7.4.2	I-2.3.7.4		n.d.	3.4	I_OJH_10_IPROP_DEA.M

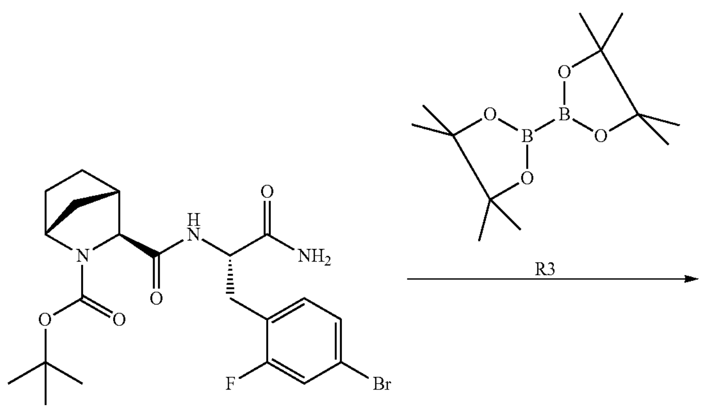
Step 4: Synthesis of Example 2

To I-2.3 (2.35 g, 4.4 mmol) in acetonitrile (50 mL) sodium iodide (1.98 g, 13 mmol) and chlorotrimethylsilane (1.44 g, 13 mmol) are added. The mixture is stirred for 1 h, then methanol is added, stirred for additional 30 min and then concentrated. The residue is purified by reversed phase HPLC. Yield 47%, m/z 433 [M+H]+, rt 0.59 min, LC-MS Method X011_S01.

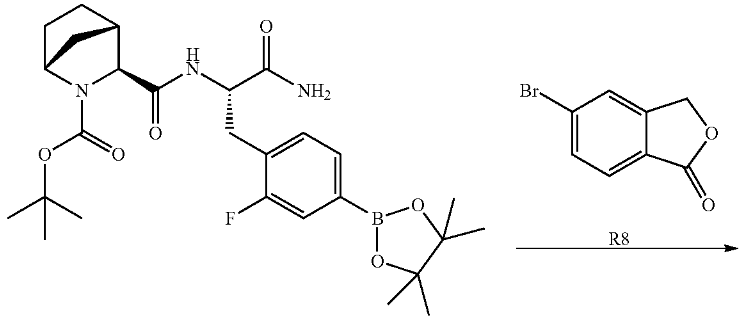
Method A2.1

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-(1-oxo-3H-isobenzofuran-5-yl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 3

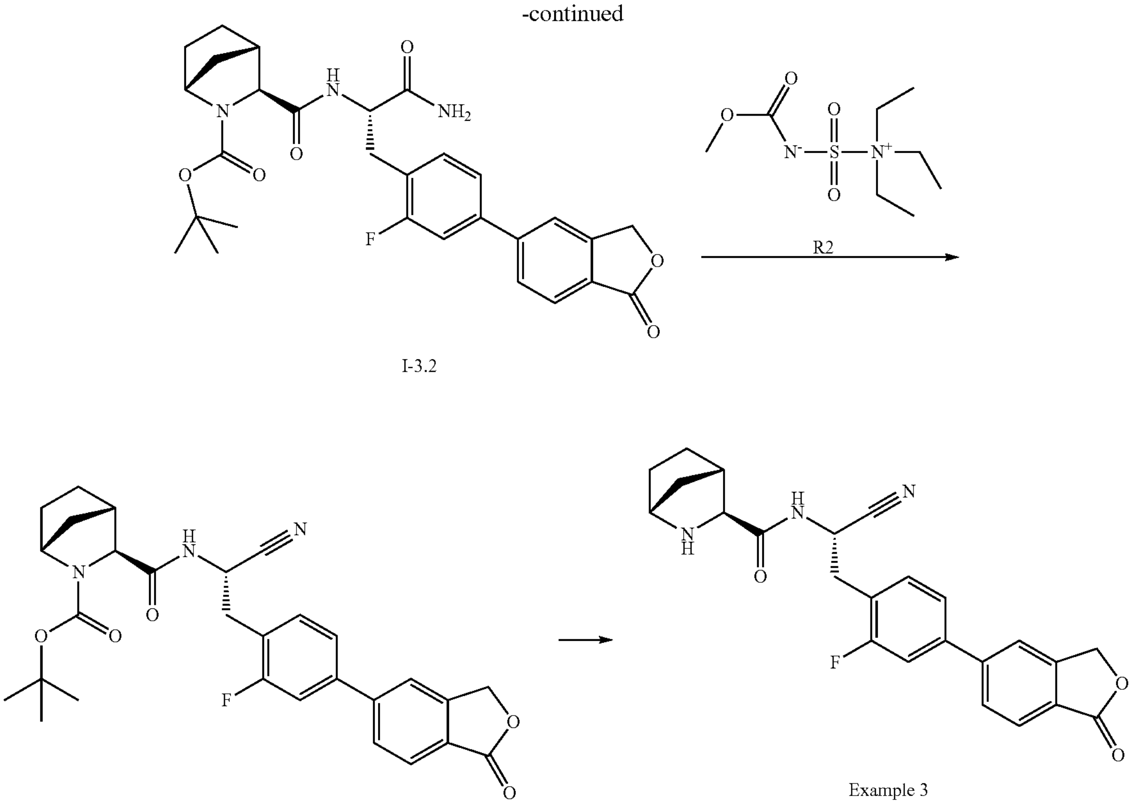


I-2.1



I-3.1

-continued



I-3.2

I-3.3

Example 3

Step 1: Synthesis of Intermediate I-3.1

To I-2.1 (1.00 g, 2.1 mmol) in dioxane (5 mL) R3 (0.58 g, 2.3 mmol) is added. The mixture is purged with argon. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) as a complex with dichloromethane (34 mg, 0.04 mmol) and potassium acetate (0.39 g, 3.9 mmol) are added. The mixture is heated to 100° C. for 12 h. Water is added to the reaction mixture, which is extracted with diethyl ether. The organic layer is washed with brine, dried over $MgSO_4$, filtrated and concentrated. Yield 74% m/z 532 [M+H]+

The following intermediates as shown in Table 12a are synthesized in a similar fashion from the appropriate intermediate:

TABLE 12a

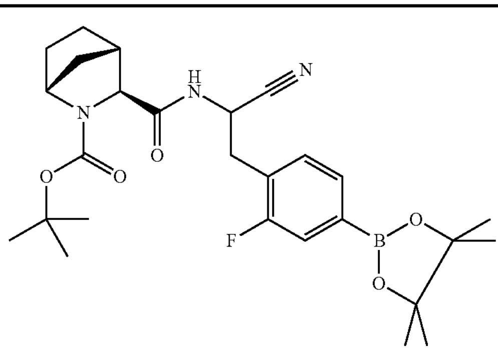
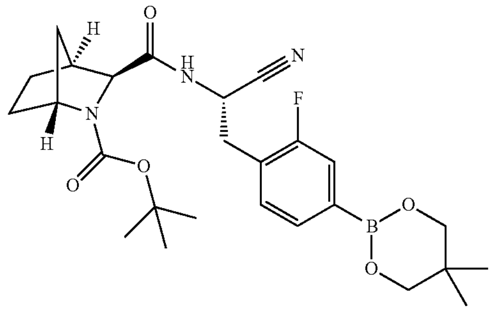
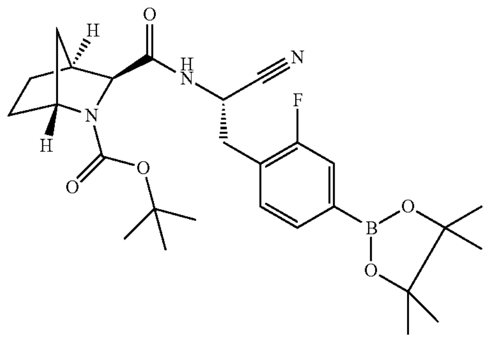
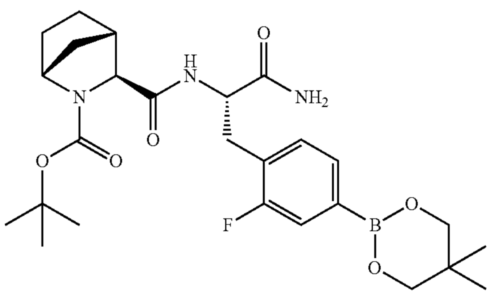
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.1.1	(1RS)-I-2.2		514	0.90	V011_S01

TABLE 12a-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.1.2	I-2.2		432	1.05	V018_S01
I-3.1.3	I-2.2		514	0.95	Z011_S03
I-3.1.5	I-2.1		450 (Boronacid)	0.67	V011_S01

During the synthesis of intermediate I-3.1.2, I-3.1.4 and I-3.1.5 instead of R3 5,5,5',5'-Tetramethyl-[2,2']bi[[1,3,2]dioxaborinanyl] is used.

During the synthesis of intermediate I-3.1 I-3.1.2 and I-3.1.4 also the corresponding boronic acid is isolated as shown in Table 12b. Either the boronic ester or boronic acid is used for the next steps.

TABLE 12b

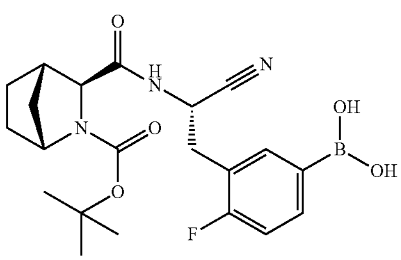
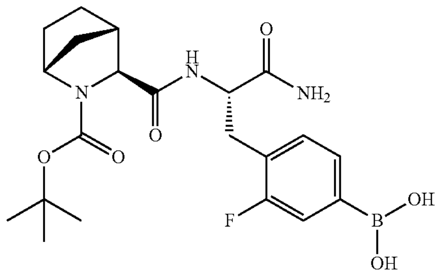
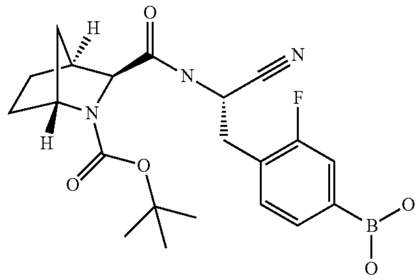
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.1.4	I-2.2.3		432	0.88	V011_S01

TABLE 12b-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.1.6	I-2.1		449	0.42	X016_S01
I-3.1.7	I-2.2		432	0.56	X018_S01

Step 2: Synthesis of Intermediate I-3.2

To I-3.1 (295 mg, 0.66 mmol, as boronic acid (I-3.1.6)) in acetonitrile (4 mL) aq. Na_2CO_3-solution (2 M, 663 μL) is added. The mixture is purged with argon, R8 (154 mg, 0.72 mmol) and [1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) as a complex with dichloromethane (80 mg, 0.10 mmol) are added. The reaction is stirred at 70° C. for 4 h. Ethyl acetate is added and the mixture is filtrated. The filtrate is washed with water and aq. Na_2CO_3 solution (10%). The organic layer is dried over $MgSO_4$ and concentrated. The residue is purified by flash chromatography (DCM/methanol=97/3). Yield 53%.

The following intermediates as shown in Table 13 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 13

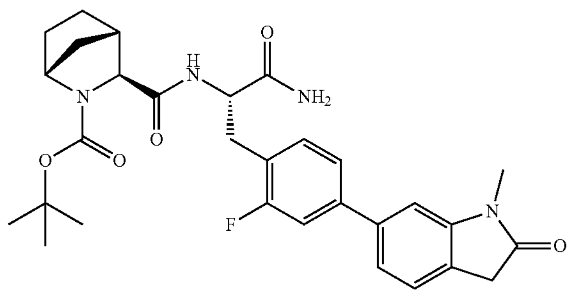
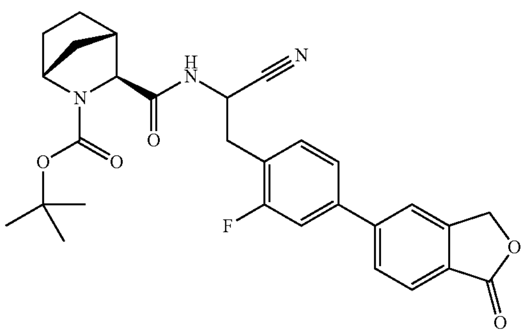
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.1	I-3.1		551	1.08	V011_S01
I-3.2.2	I-3.1.1		520	1.21	V011_S01

TABLE 13-continued

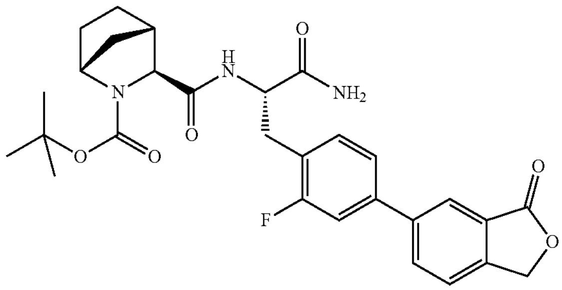
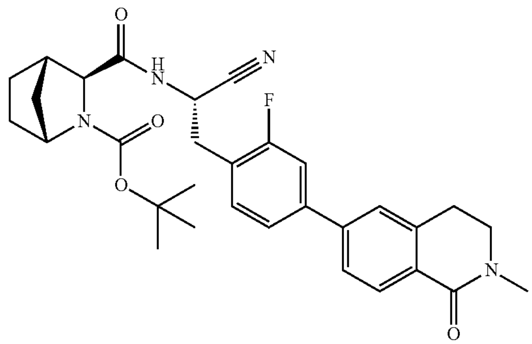
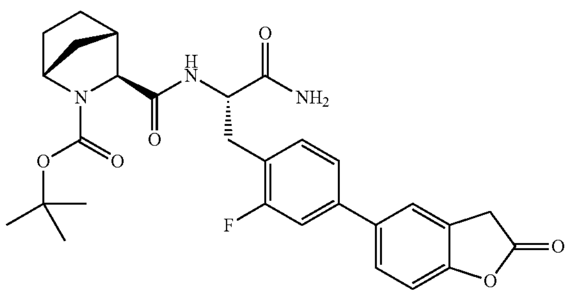
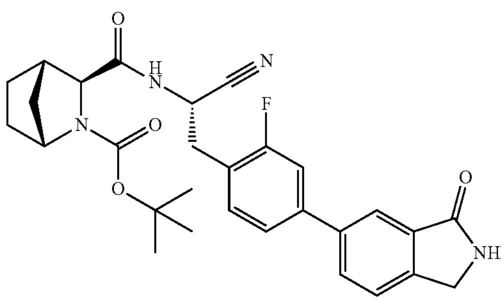
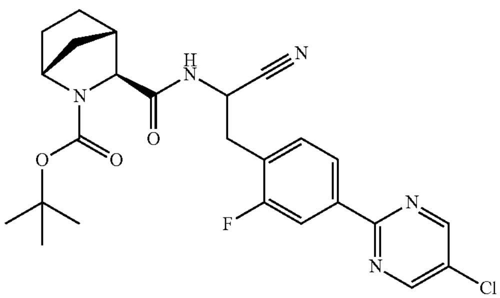
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.5	I-3.1		n.d.	n.d.	n.d.
I-3.2.6	(1S)-I-3.1.1		447/ 491/ 547	1.18	V011_S01
I-3.2.8	I-3.1		n.d.	n.d.	n.d.
I-3.2.10	(1S)-I-3.1.1		519	1.11	V011_S01
I-3.2.11	I-3.1.1		n.d.	n.d.	n.d.

TABLE 13-continued

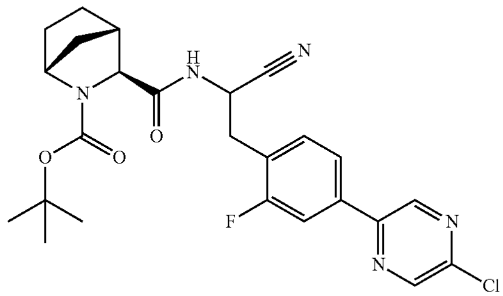
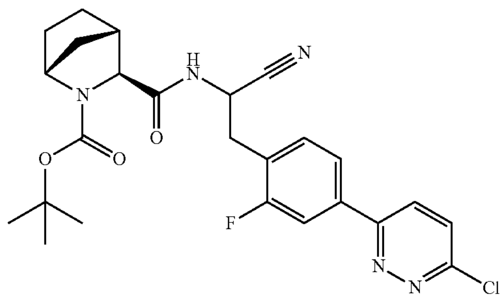
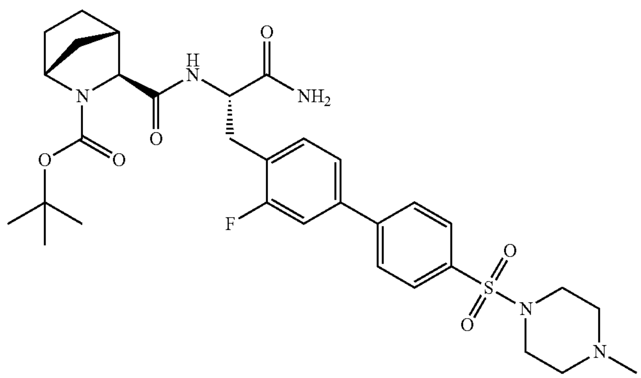
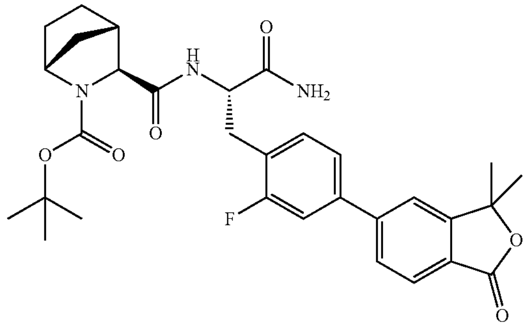
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.12	I-3.1.1		n.d.	n.d.	n.d.
I-3.2.13	I-3.1.1		n.d.	n.d.	n.d.
I-3.2.15	I-3.1		n.d.	n.d.	n.d.
I-3.2.16	I-3.1		n.d.	n.d.	n.d.

TABLE 13-continued

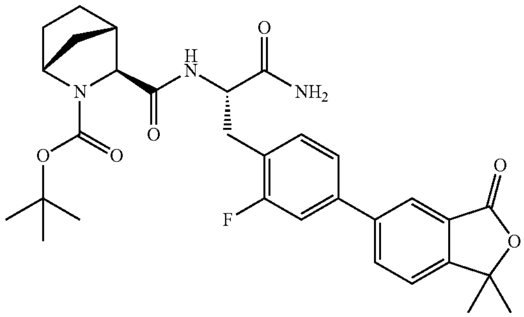
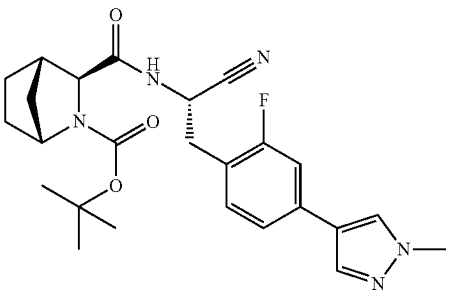
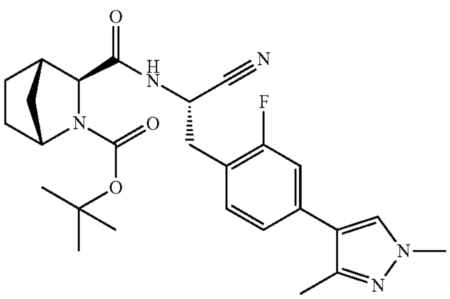
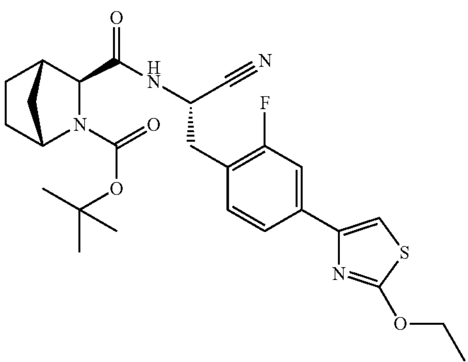
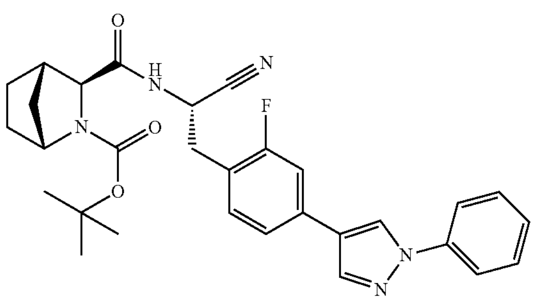
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.17	I-3.1		n.d.	n.d.	n.d.
I-3.2.36	I-3.1.3		368 (M + H − BOC)+	0.73	004_CA05
I-3.2.37	I-3.1.3		382 (M + H − BOC)+	0.75	004_CA05
I-3.2.38	I-3.1.3		415 (M + H − BOC)+	0.95	004_CA05
I-3.2.39	I-3.1.3		430 (M + H − BOC)+	0.91	004_CA05

TABLE 13-continued

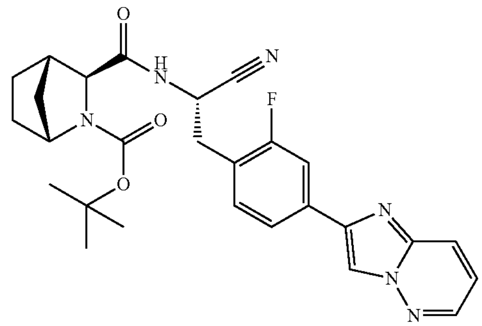
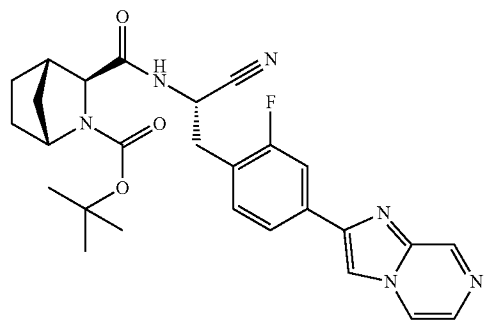
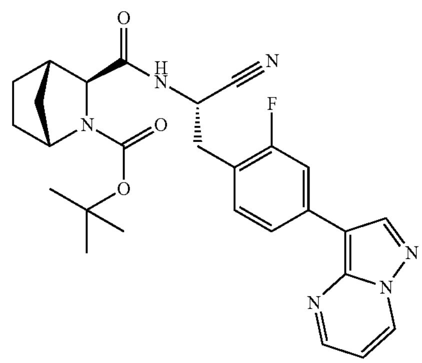
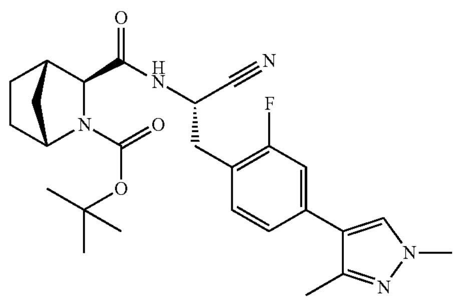
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.40	I-3.1.3		405 (M + H − BOC)+	0.74	004_CA05
I-3.2.41	I-3.1.3		405 (M + H − BOC)+	0.67	004_CA05
I-3.2.42	I-3.1.3		405 (M + H − BOC)+	0.77	004_CA05
I-3.2.43	I-3.1.3		382 (M + H − BOC)+	0.72	004_CA05

TABLE 13-continued

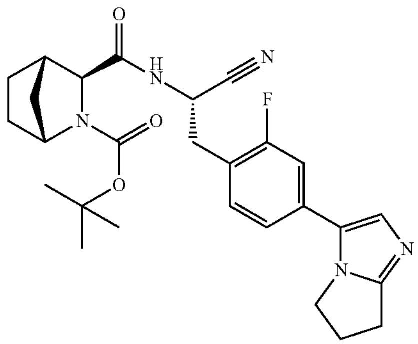
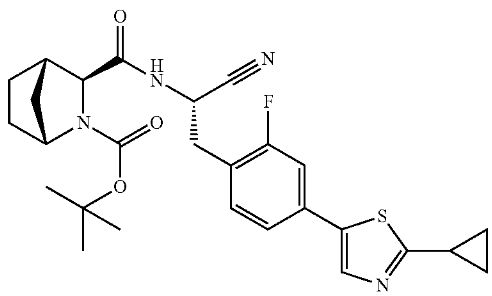
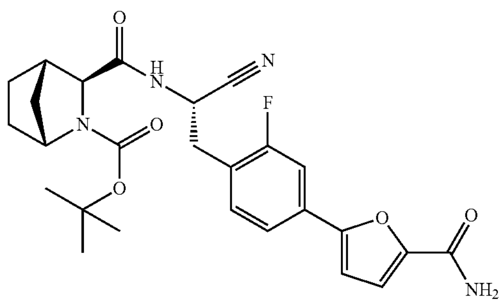
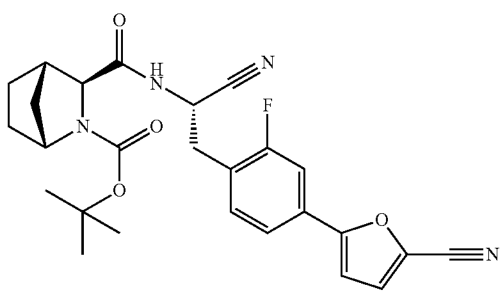
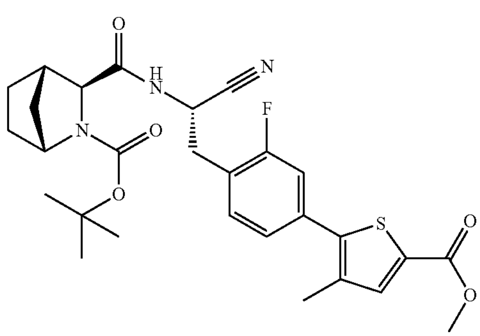
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.44	I-3.1.3		394 (M + H − BOC)+	0.70	004_CA05
I-3.2.45	I-3.1.3		411 (M + H − BOC)+	0.88	004_CA05
I-3.2.46	I-3.1.3		397 (M + H − BOC)+	0.68	004_CA05
I-3.2.47	I-3.1.3		379 (M + H − BOC)+	0.85	004_CA05
I-3.2.48	I-3.1.3		442 (M + H − BOC)+	0.92	004_CA05

TABLE 13-continued

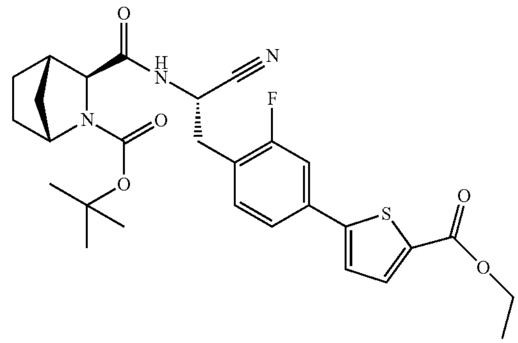
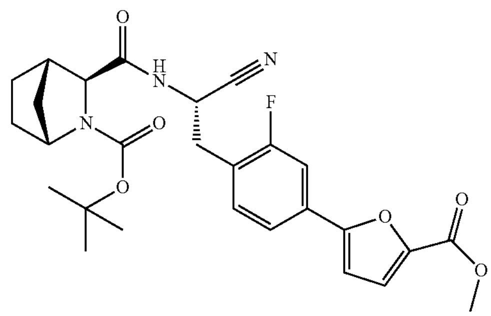
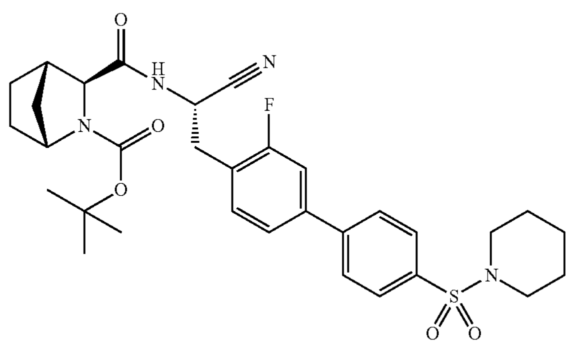
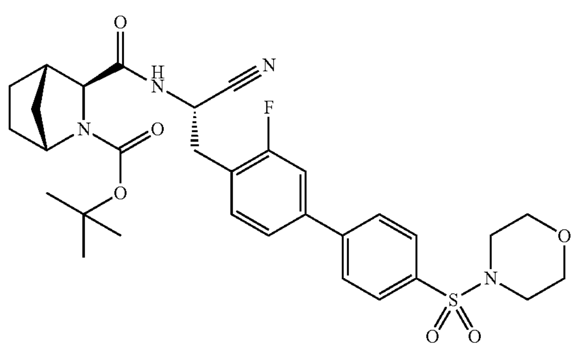
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.49	I-3.1.3		442 (M + H − BOC)+	0.94	004_CA05
I-3.2.50	I-3.1.3		412 (M + H − BOC)+	0.84	004_CA05
I-3.2.51	I-3.1.3		611	n.d.	n.d.
I-3.2.52	I-3.1.3		613	1.24	V012_S01

TABLE 13-continued

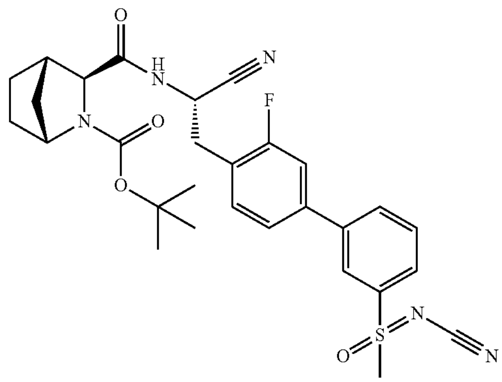
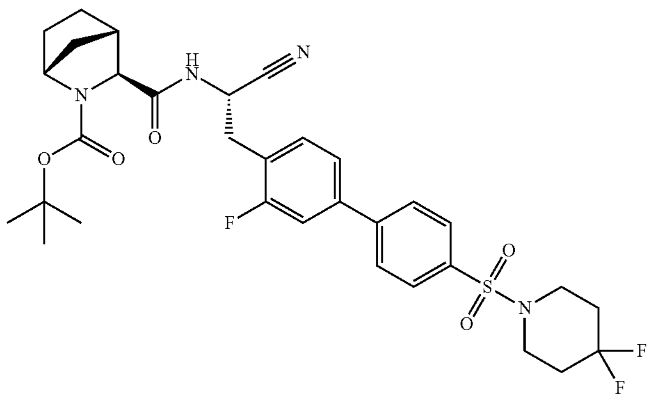
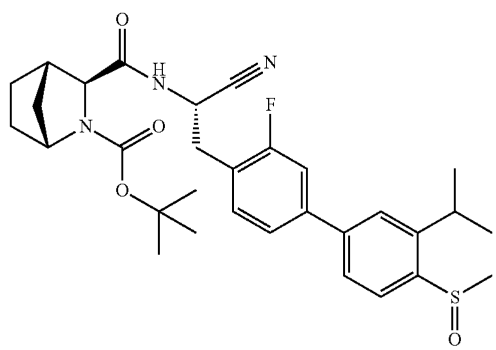
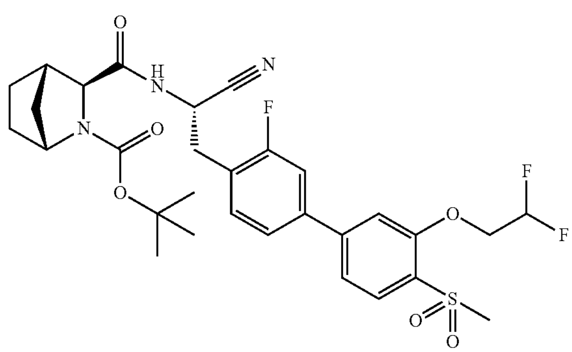
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.53	I-3.1.3		466 (M + H − BOC)+	0.91	Z018_S04
I-3.2.54	I-3.1.3		647	n.d.	n.d.
I-3.2.55	I-3.1.2		568	1.23	V011_S01
I-3.2.56	I-3.1.2		622	1.24	V011_S01

TABLE 13-continued

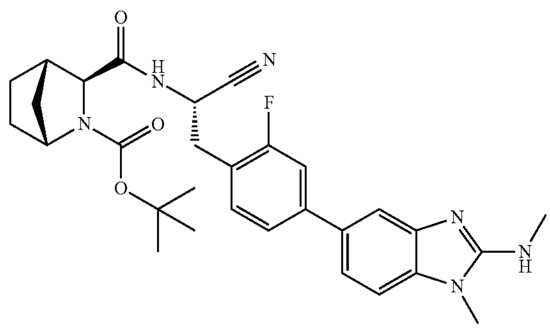
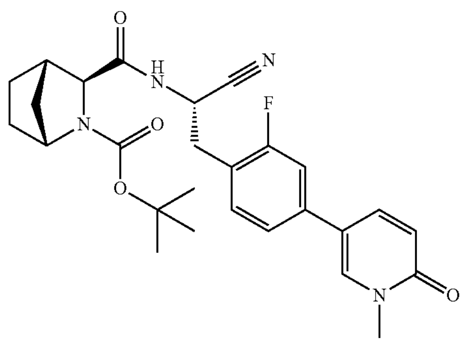
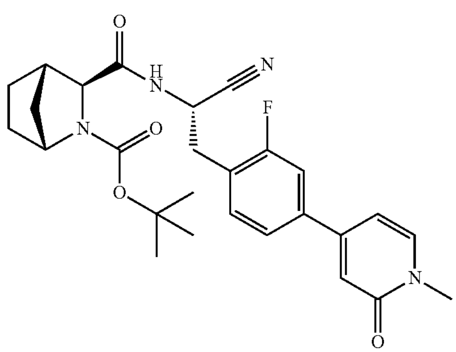
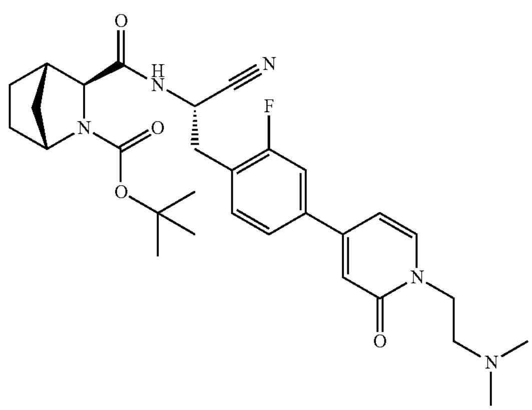
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.57	I-3.1.2		547	0.76	X011_S03
I-3.2.58	I-3.1.2		494	0.57	X011_S03
I-3.2.59	I-3.1.2		494	0.56	X011_S03
I-3.2.60	I-3.1.2		552	0.58	X011_S03

TABLE 13-continued

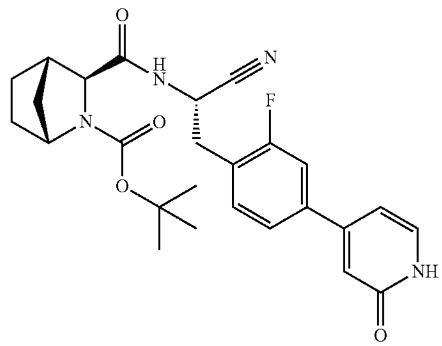
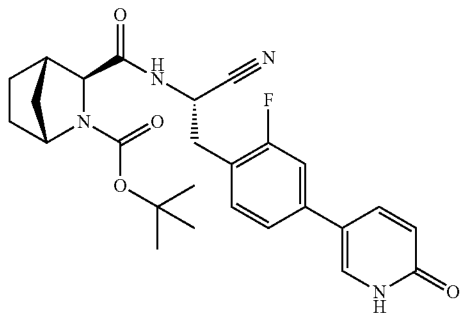
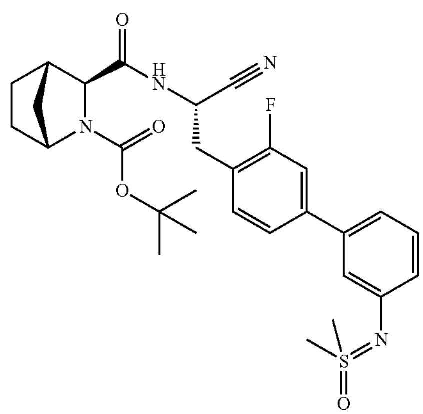
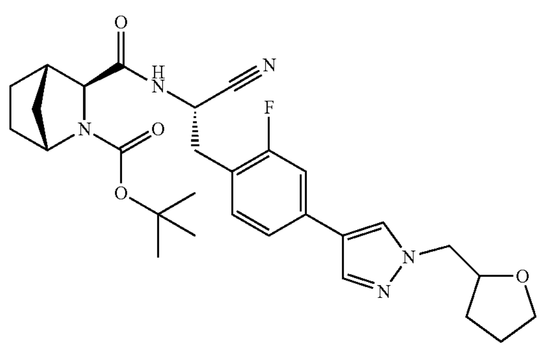
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.61	I-3.1.2		380 (M + H − BOC)+	0.52	X011_S03
I-3.2.62	I-3.1.2		380 (M + H − BOC)+	0.52	X011_S03
I-3.2.63	I-3.1.3		445 (M + H − BOC)+	0.93	Z018_S04
I-3.2.64	I-3.1.3		538	0.94	Z018_S04

TABLE 13-continued

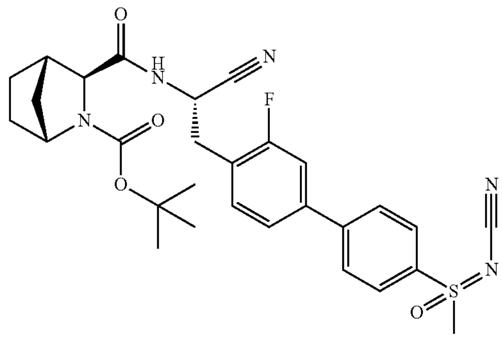
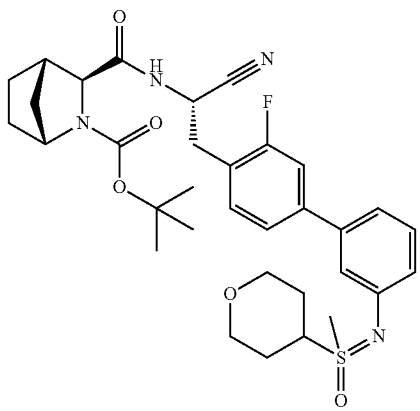
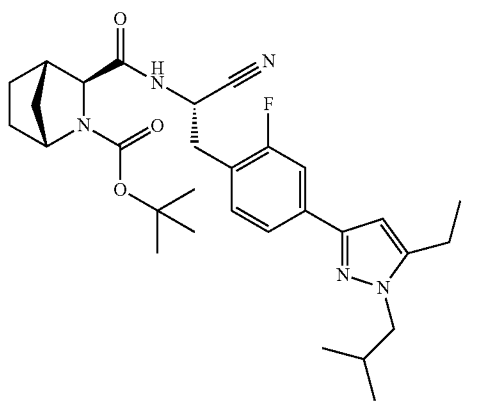
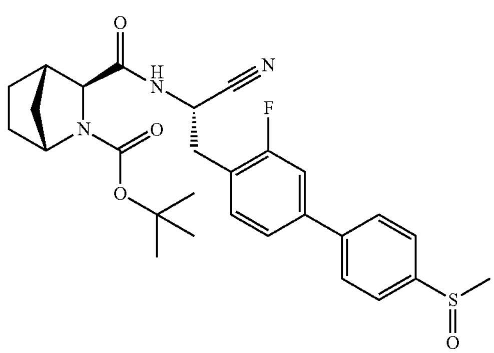
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.65	I-3.1.3		466 (M + H − BOC)+	0.91	Z018_S04
I-3.2.66	I-3.1.3		525 (M + H − BOC)+	0.93	Z011_S03
I-3.2.67	I-3.1.7		538	0.83	X018_S01
I-3.2.68	I-3.1.7		526	1.11	V011_S01

TABLE 13-continued

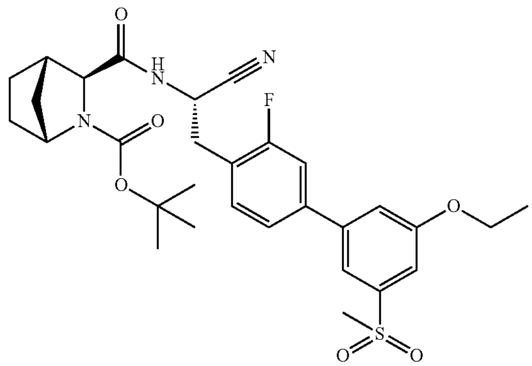
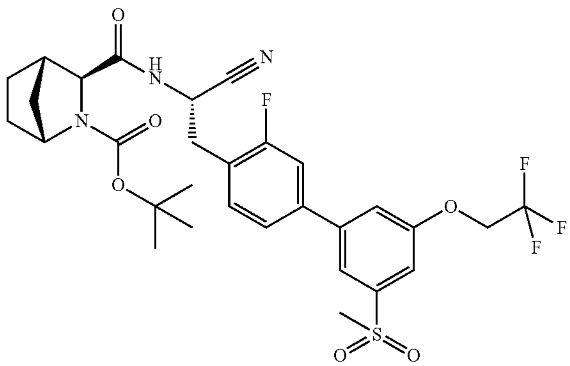
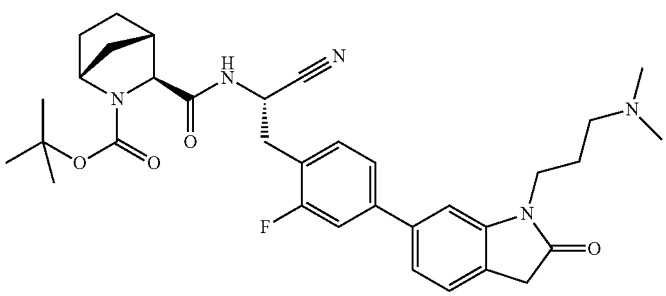
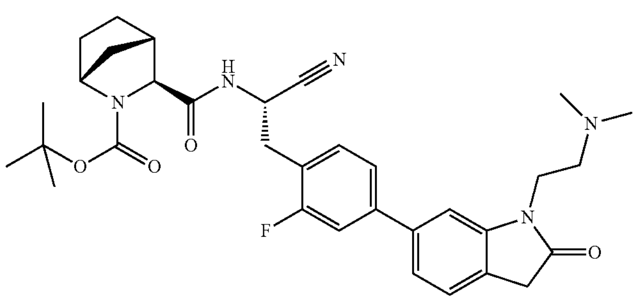
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.69	I-3.1.7		586	1.29	V011_S01
I-3.2.70	I-3.1.7		640	1.31	V011_S01
I-3.2.71	I-3.1.7		604	n.d.	n.d.
I-3.2.72	I-3.1.7		n.d.	n.d.	n.d.

TABLE 13-continued

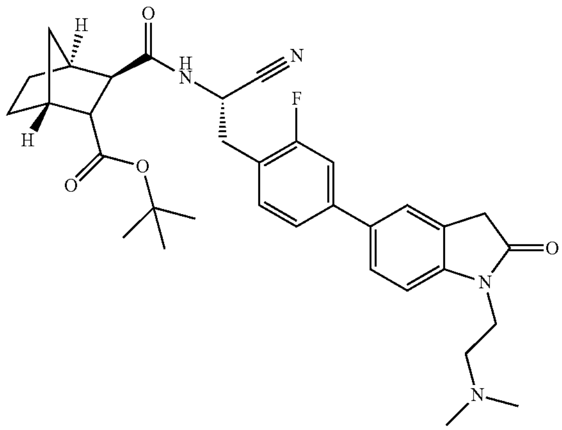
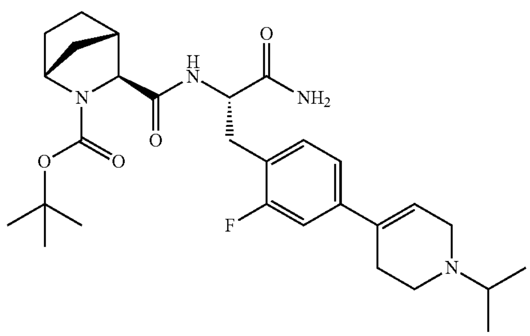
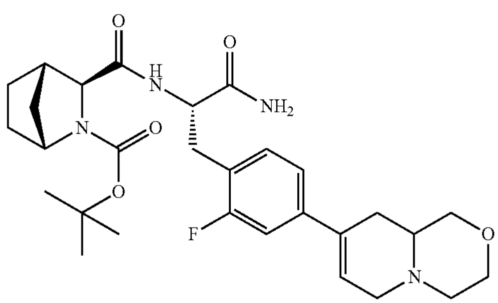
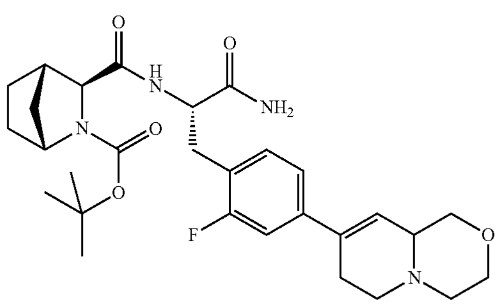
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.73	I-3.1.7		590	1.03	Z011_S03
I-3.2.74	I-3.1		529	0.48	X012_S02
I-3.2.75	I-3.1		543	1.04	V011_S01
I-3.2.76	I-3.1		543	1.02	V011_S01

TABLE 13-continued

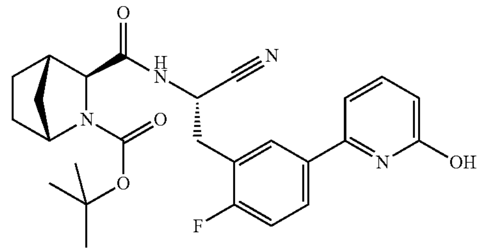
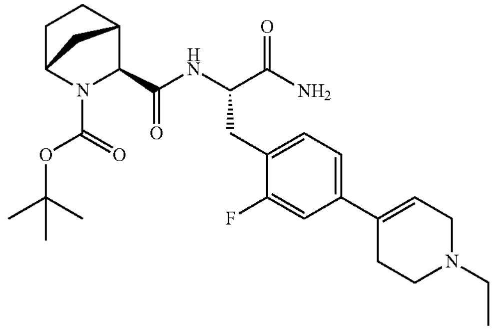
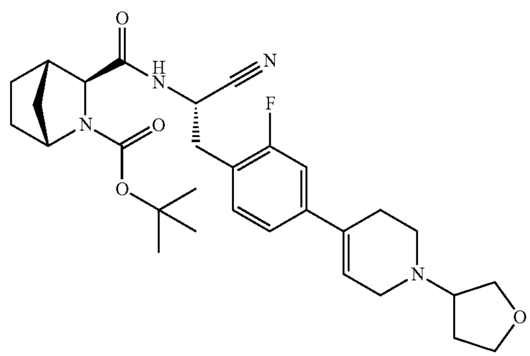
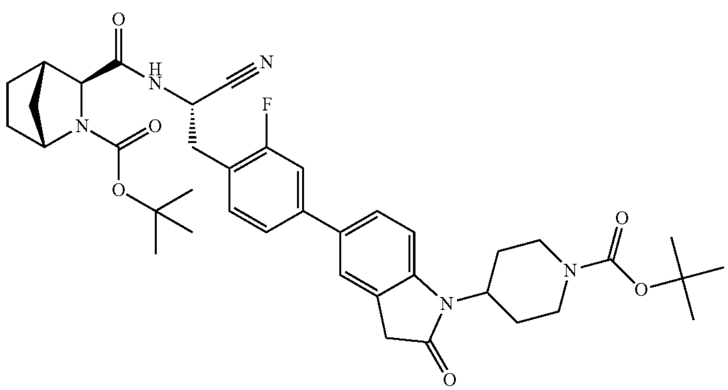
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.77	I-3.1.4		n.d.	n.d.	n.d.
I-3.2.78	I-3.1		n.d.	n.d.	n.d.
I-3.2.79	I-3.1.7		539	1.18	V011_S01
I-3.2.80	I-3.1.7		546 (M + H − Boc-t-Bu)	1.106	Z020_S01

TABLE 13-continued

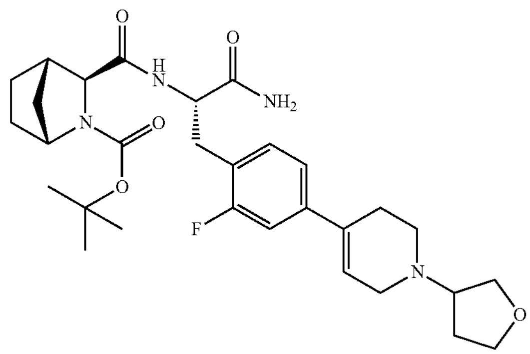
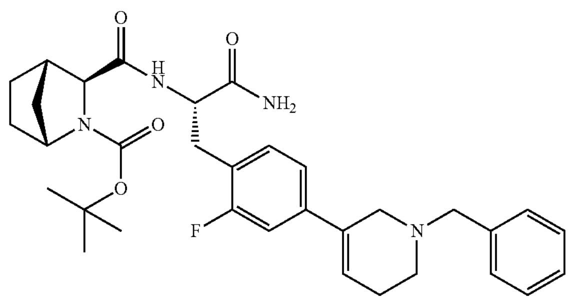
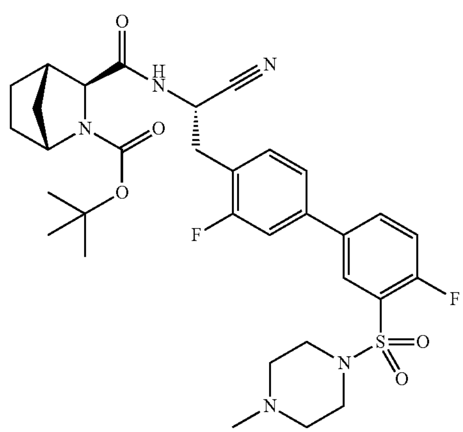
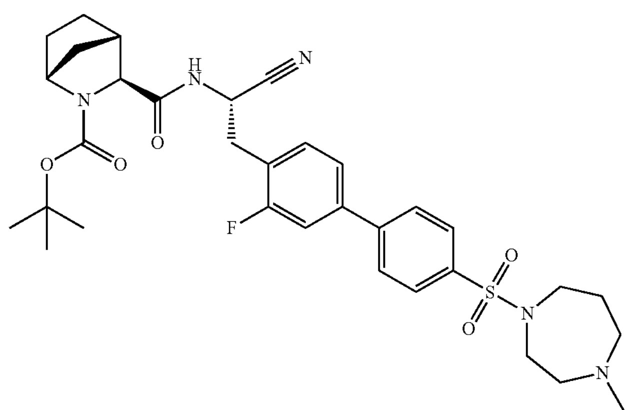
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.81	I-3.1.6		557	1.05	V011_S01
I-3.2.82	I-3.1.6		577	0.50	X018_S02
I-3.2.83	I-3.1.1		644	0.53	X012_S01
I-3.2.84	I-3.1.7		640	0.53	X012_S01

TABLE 13-continued

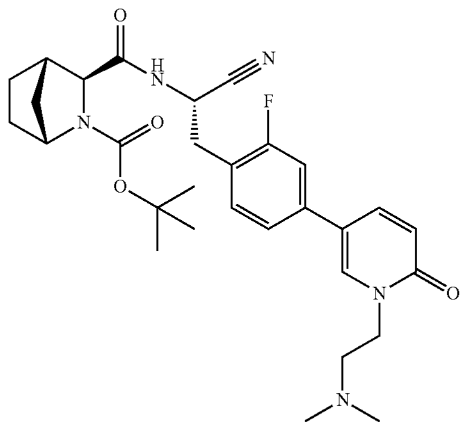
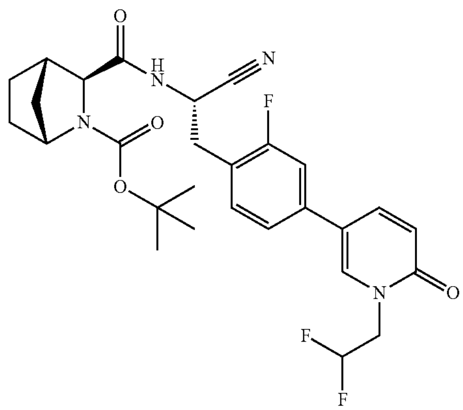
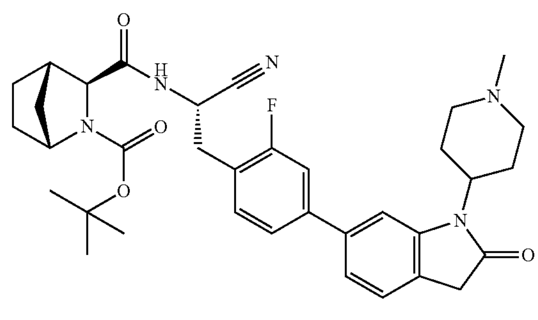
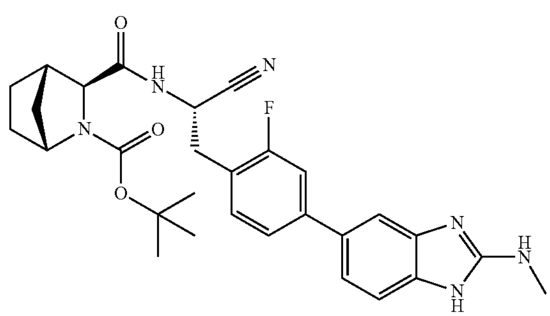
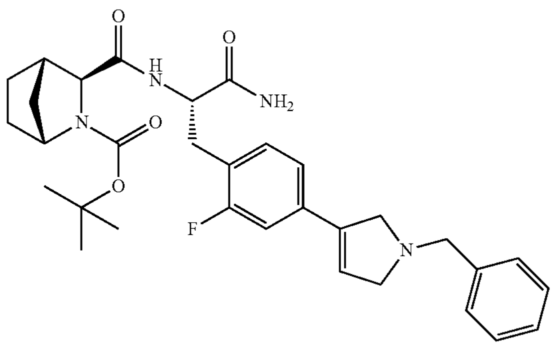
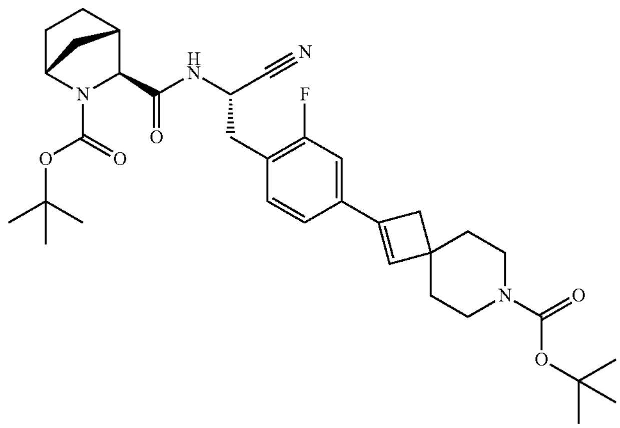
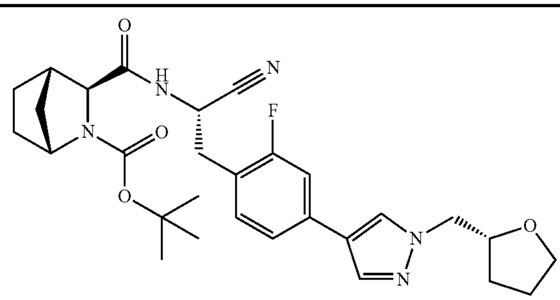
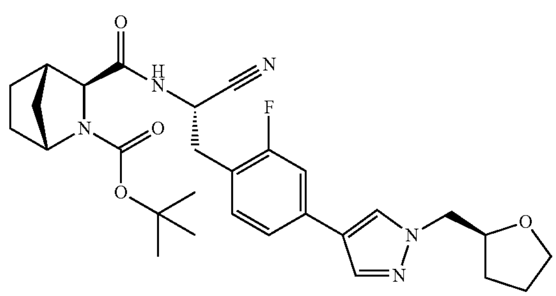
Inter-mediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.85	I-3.1.7		551	0.59	X011_S03
I-3.2.86	I-3.1.7		544	0.60	X012_S02
I-3.2.87	I-3.1.7		n.d.	n.d.	n.d.
I-3.2.88	I-3.1.2		533	1.08	V011_S01

TABLE 13-continued

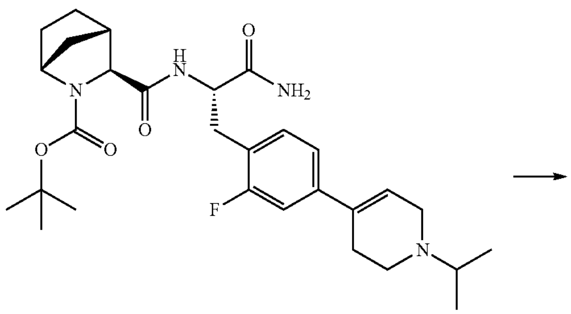
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.90	I-3.1.6		563	1.29	V011_S01
I-3.2.91	I-3.1.7		n.d.	n.d.	n.d.

Intermediate I-3.2.64 is separated according to method chiral SFC A to give the following intermediates as shown in Table 13.1

TABLE 13.1

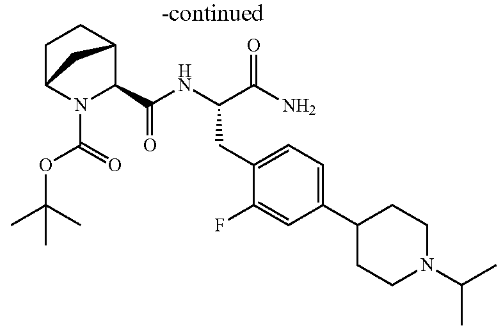
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.64.1	I-3.2.64		n.d.	3.828	I_ADH_15_MEOH_DEA.M
I-3.2.64.2	I-3.2.64		n.d.	4.631	I_ADH_15_MEOH_DEA.M

Intermediate I-3.2.74, I-3.2.75, I-3.2.81, I-3.2.82, I-3.2.89, I-3.2.90, I-3.2.113, is further processed via hydrogenation before the BOC group is removed (step 4)



I-3.2.74

-continued



I-3.2.130

To I-3.2.74 (210 mg, 0.33 mmol) in methanol (10 mL) Pd/C (10%, 90 mg) is added. The reaction mixture is stirred at 50° C. under hydrogen (50 psi) for 6 h. Then the mixture is filtered and concentrated. The crude product is carried on with step 4. Yield 85%, m/z 531 [M+H]+, rt 0.48 min, LC-MS Method X012_S02.

In analogy the following intermediates as shown in Table 17 are prepared.

TABLE 17

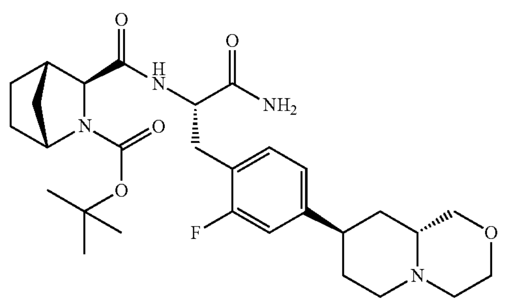
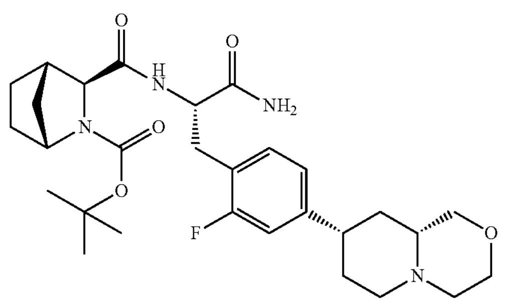
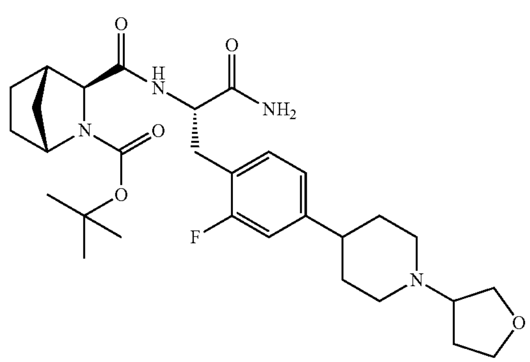
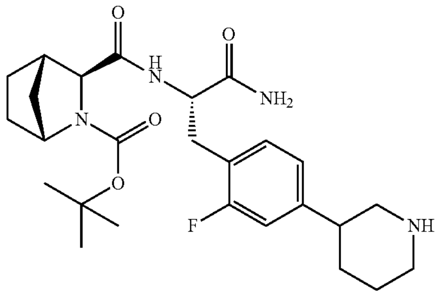
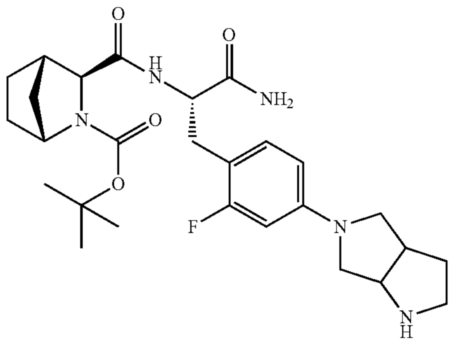
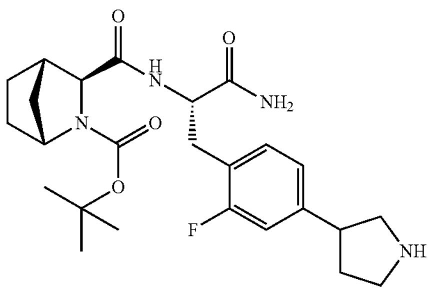
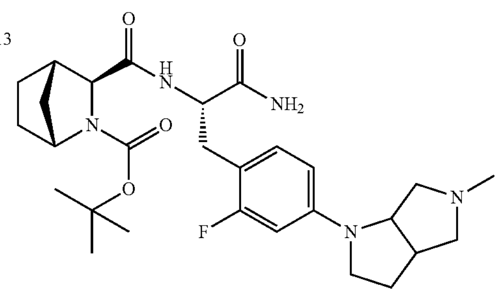
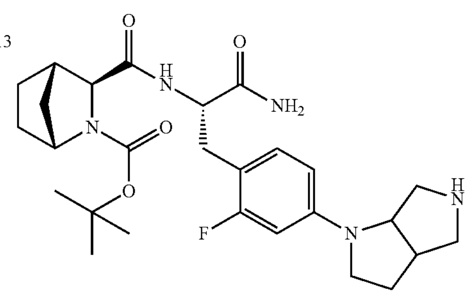
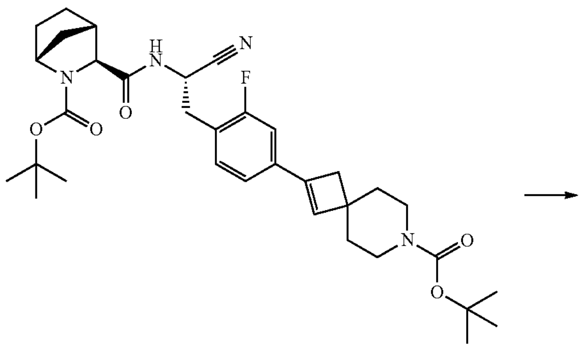
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.122	I-3.2.75		545	0.98	V011_S01
I-3.2.123	I-3.2.75		545	1.03	V011_S01
I-3.2.124	I-3.2.81		559	0.62	X011_S03

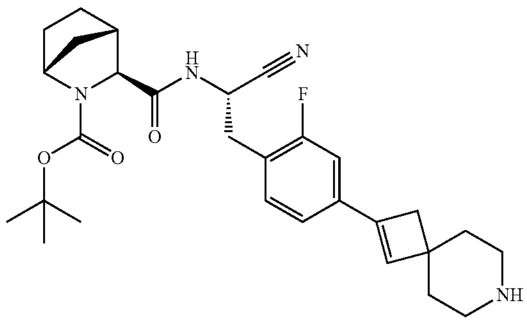
TABLE 17-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.125	I-3.2.82		489	0.44	X018_S02
I-3.2.126	I-3.2.89		516	1.02	V011_S01
I-3.2.127	I-3.2.90		475	0.41	X018_S02
I-3.2.128	I-3.2.113		530	1.12	V011_S01
I-3.2.129	I-3.2.113		530	1.00	V011_S01

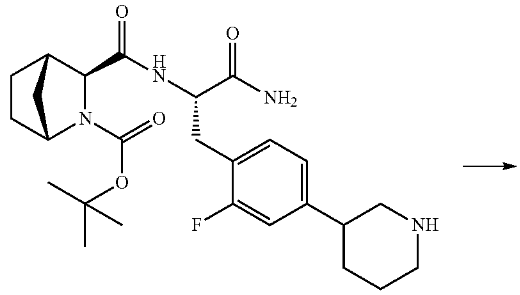
Intermediate I-3.2.91 is further processed in the following way:



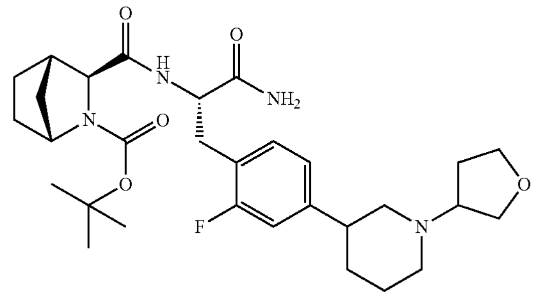
I-3.2.91



I-3.2.131



I-3.2.125



I-3.2.132

To I-3.2.91 (200 mg, 0.28 mmol) in ACN (3 mL) is added p-toluene sulfonic acid monohydrate (79.67 mg, 0.42 mmol) and stirred at r.t. for 2.5 h. The reaction mixture is diluted with TEA, filtered and purified by reversed phase HPLC.

Yield 68%

Intermediate I-3.2.125, I-3.2.126, I-3.2.129 and I-3.2.131 is further processed via reductive amination before the BOC group is removed (step 4)

To I-3.2.125 (130 mg, 0.266 mmol) in dichlormethane is added 3-oxotetrahydrofuran (27.49 mg, 0.319 mmol) and glacial acetic acid (15.22 μL, 0.266 mmol) and stirred for 45 min at r.t. Sodium triacetoxyborohydride (83.1 mg, 0.372 mmol) is added and the reaction mixture is stirred at r.t. overnight.

The reaction mixture is diluted with dichlormethane and sat. $NaHCO_3$. The organic layer is separated, dried and concentrated. The crude product is used for the next step without further purification.

Yield 99%, m/z 559 [M+H]+, rt 0.44 min, LC-MS Method X018_S02.

In analogy the following intermediates as shown in Table 18 are prepared.

TABLE 18

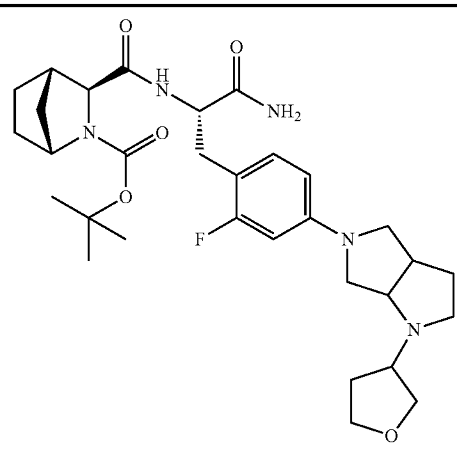
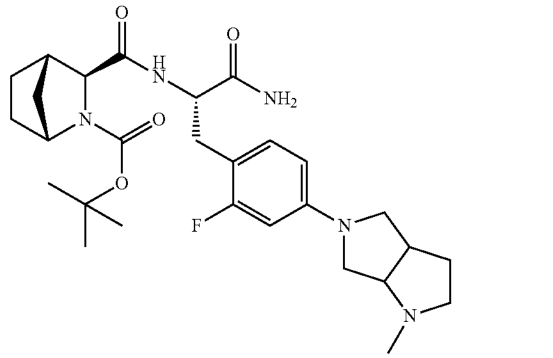
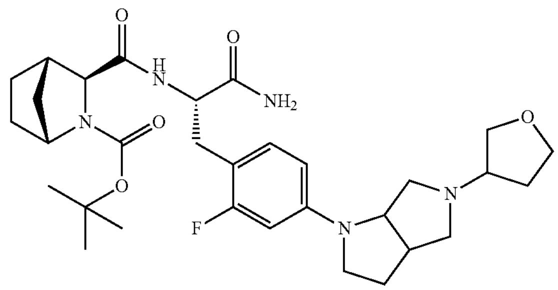
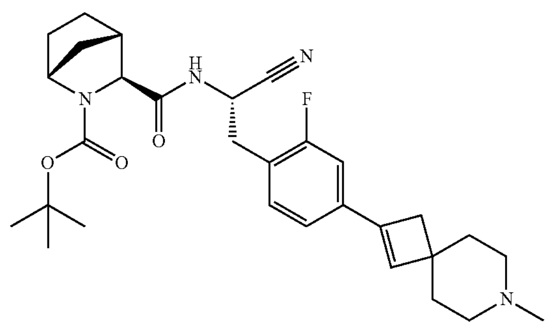
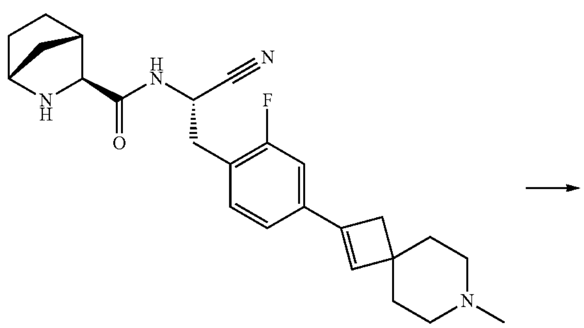
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.133,	I-3.2.126,		586	0.50	X012_S02

TABLE 18-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.134	I-3.2.126		530	1.14	V011_S01
I-3.2.135	I-3.2.129		586	1.09	V011_S01
I-3.2.136	I-3.2.131		n.d.	n.d.	n.d.

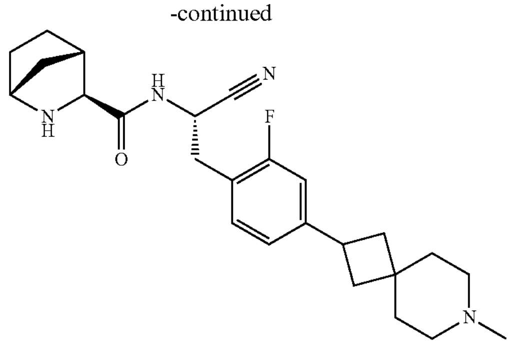
The reaction time for I-3.2.133 and I-3.2.135 is 30 min at r.t. and for I-3.2.134 2 h at r.t. and for I-3.2.136 1 h at r.t.

Intermediate I-3.2.136 is deprotected (see example 359) and further processes via hydrogenation to give example 358:



Example 359

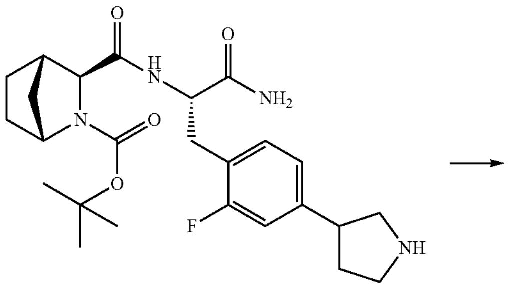
-continued



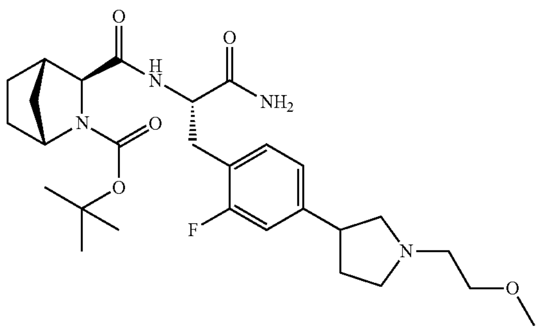
Example 358

To example 359 (20 mg, 0.047 mmol) in methanol (3 mL) Pd/C (10%, 5 mg) is added. The reaction mixture is stirred at r.t. under hydrogen (50 psi) for 10 min. Then the mixture is filtered and concentrated. The crude product is purified by reversed phase HPLC to give example 358. Yield 35%, m/z 425 [M+H]+, rt 0.715 min, LC-MS Method Z012_S04.

Intermediate I-3.2.127 is further processed via alkylation before the BOC group is removed (step 4)



I-3.2.127



I-3.2.137

To I-3.2.127 (71 mg, 0.15 mmol) in DMF (2 mL) is added 2-bromoethyl methyl ether (29.53 μL, 0.31 mmol) and potassium carbonate (41.36, 0.266 mmol) and stirred overnight at r.t. The reaction mixture is diluted with dichlormethane and water. The organic layer is separated, dried and concentrated. The crude product is purified by reversed phase HPLC. Yield 40%, m/z 533 [M+H]+, rt 1.05 min, LC-MS Method V011_S01.

Step 3: Synthesis of Intermediate I-3.3

To I-3.2 (187 mg, 0.35 mmol) in DCM (12 mL) R2 (182 mg, 0.77 mmol) is added. The reaction mixture is stirred for 12 h, concentrated, dissolved in ethyl acetate and extracted with 0.1M HCl and water. The organic layer is dried over $MgSO_4$ and concentrated. Yield 86%.

The following intermediates as shown in Table 19 are synthesized in a similar fashion from the appropriate intermediate:

TABLE 19

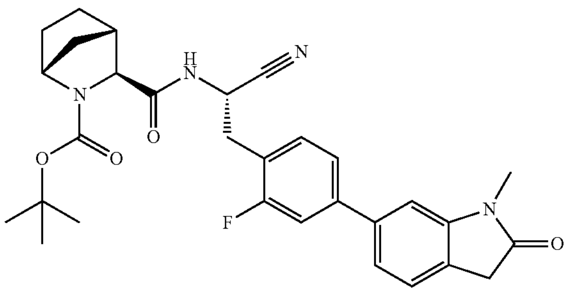
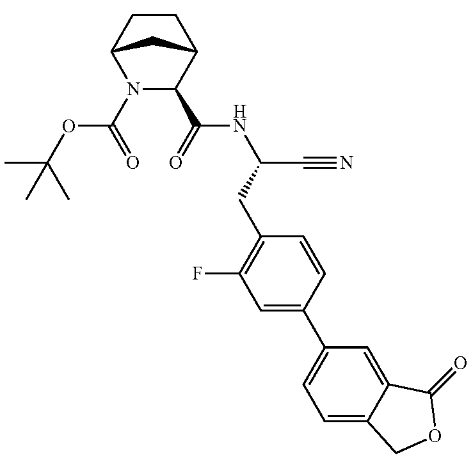
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.3.1	I-3.2.1		533	1.21	V011_S01
I-3.3.3	I-3.2.5		n.d.	n.d.	n.d.

TABLE 19-continued

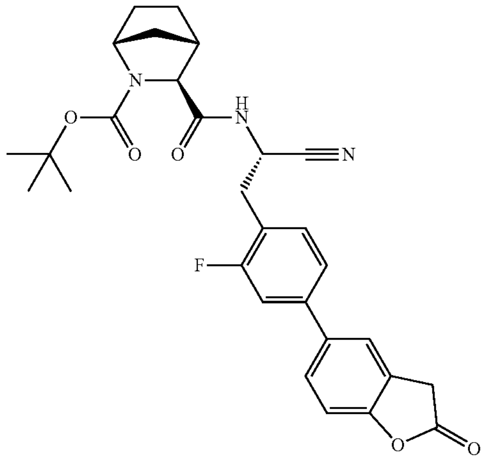
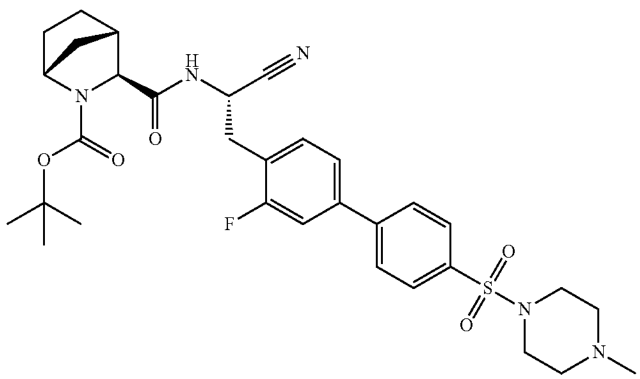
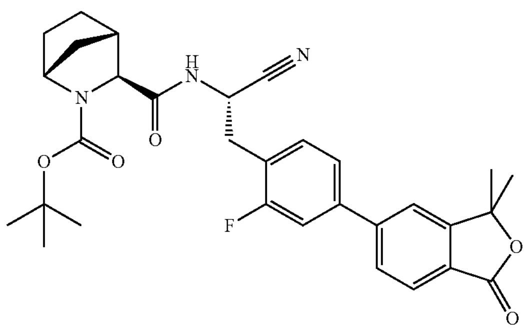
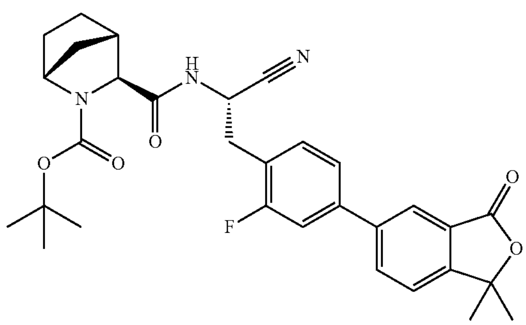
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.3.4	I-3.2.8		n.d.	n.d.	n.d.
I-3.3.5	I-3.2.15		626	n.d.	n.d.
I-3.3.6	I-3.2.16		n.d.	n.d.	n.d.
I-3.3.7	I-3.2.17		n.d.	n.d.	n.d.

TABLE 19-continued

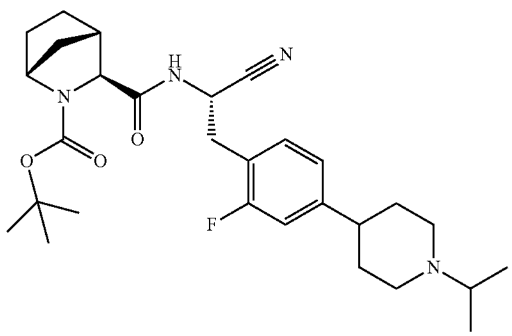
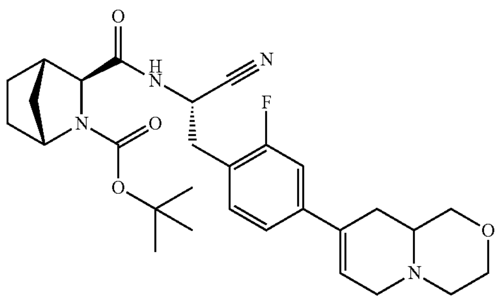
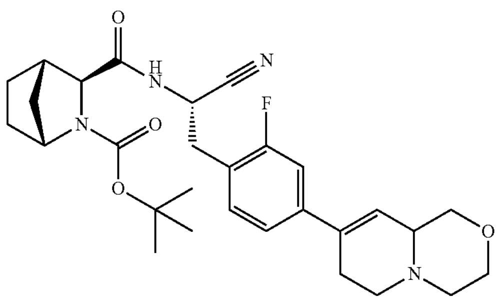
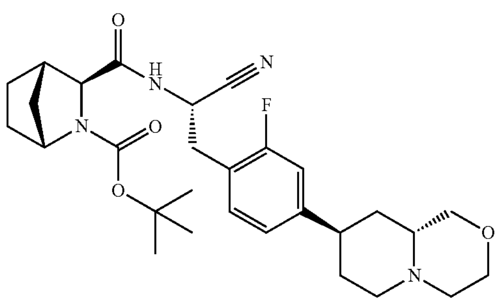
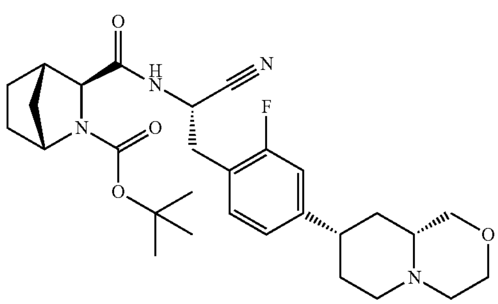
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.3.8	I-3.2.130		513	0.55	V011_S02
I-3.3.9	I-3.2.75		525	1.17	V011_S01
I-3.3.10	I-3.2.76		525	1.15	V011_S01
I-3.3.11	I-3.2.122		527	1.15	V011_S01
I-3.3.12	I-3.2.123		527	1.12	V011_S01

TABLE 19-continued

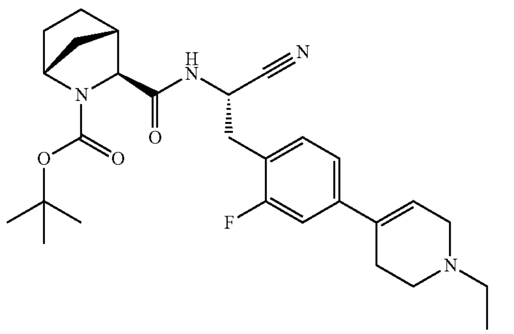
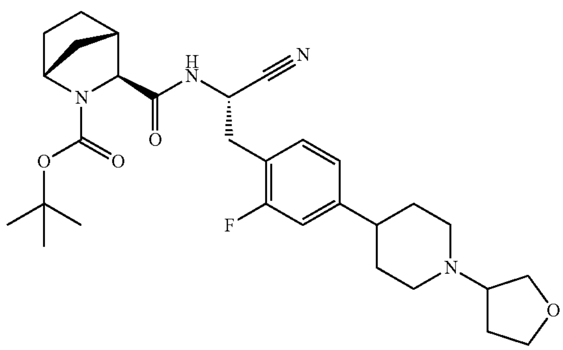
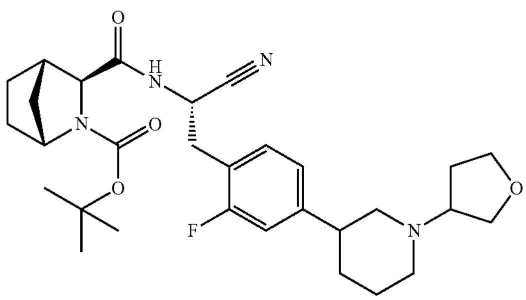
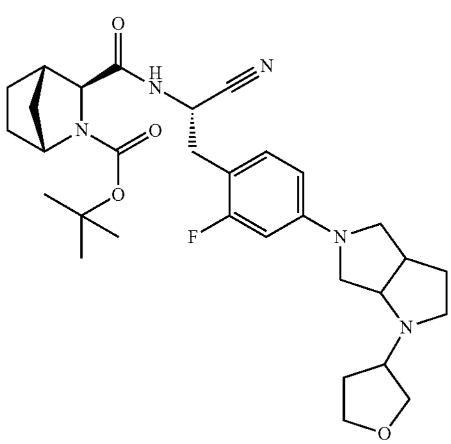
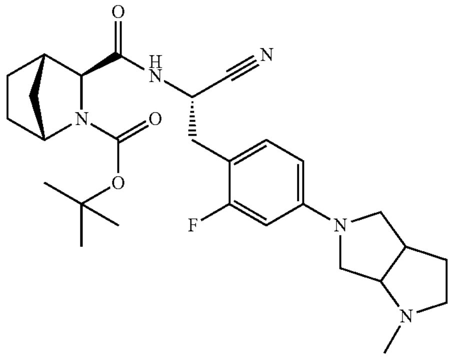
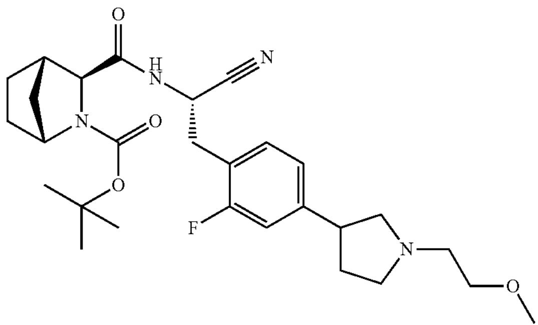
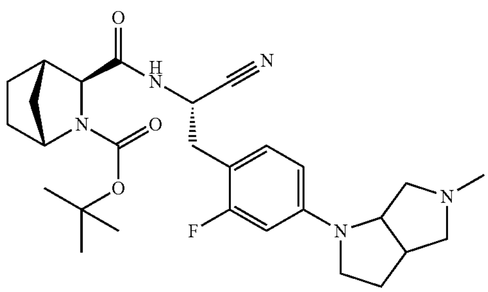
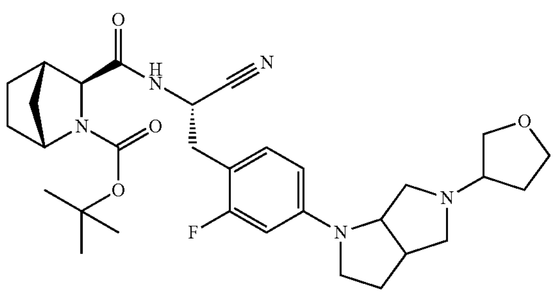
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.3.13	I-3.2.78		496	0.54	X012_S02
I-3.3.14	I-3.2.124		541	0.71	X011-S03
I-3.3.15;	I-3.2.132		541	0.49	X018_S02
I-3.3.16	I-3.2.133		568	1.22	V011_S01

TABLE 19-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.3.17	I-3.2.134		512	1.26	V011_S01
I-3.3.18	I-3.2.137		515	1.17	V011_S01
I-3.3.19	I-3.2.128		512	1.25	V011_S01
I-3.3.20	I-3.2.135		568	1.23	V011_S01

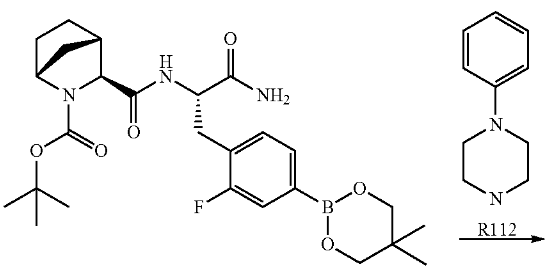
Step 4: Synthesis of Example 3

To I-3.3 (155 mg, 0.30 mmol) in acetonitrile, sodium iodide (134 mg, 0.89 mmol) and chlorotrimethylsilane (114 μl, 0.89 mmol) are added. The mixture is stirred for 2 h, then methanol is added, stirred for additional 30 min and then concentrated. The residue is purified by reversed phase HPLC. Yield 62%, m/z 420 [M+H]+, rt 0.41 min, LC-MS Method X016_S01.

Method A2.2

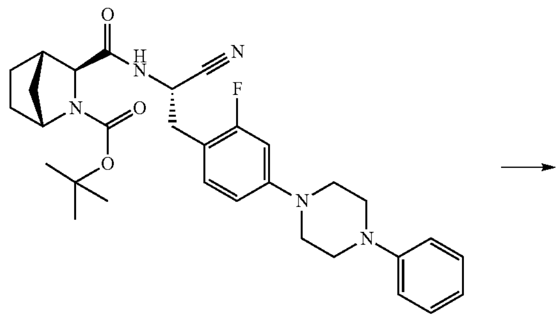
Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-(4-phenylpiperazin-1-yl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 32

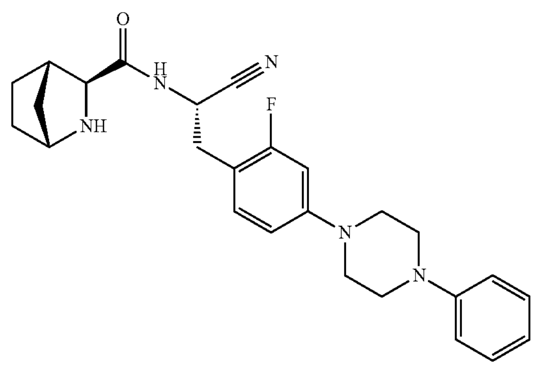


I-3.1.2

-continued



I-3.2.4



Step 1: Synthesis of Intermediate I-3.2.4

To I-3.1.2 (150 mg, 0.30 mmol) in DCM (6 mL), triethylamine (85 μL, 0.61 mmol), R112 (55.22 mg, 0.34 mmol) and copper(II)acetate (85 mg, 0.47 mmol) are added. The mixture is stirred for 72 h at r.t. 7M ammonium solution in methanol is added, the mixture is concentrated. The residue dissolved in acetonitrile and filtrated. The product is purified by reversed phase HPLC. Yield 54%, m/z 548 [M+H]+, rt 1.37 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 14 are synthesized in a similar fashion from the appropriate intermediate

TABLE 14

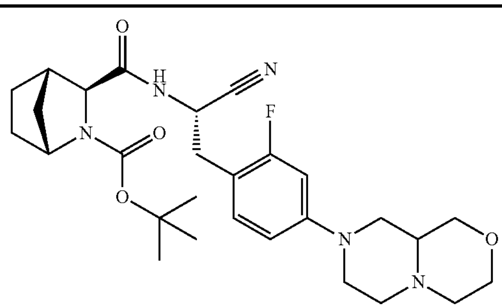
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.7	I-3.1.2		528	1.10	V011_S01

TABLE 14-continued

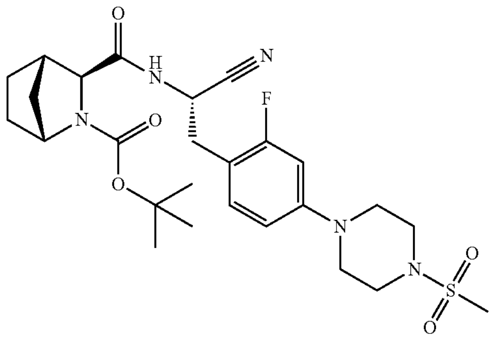
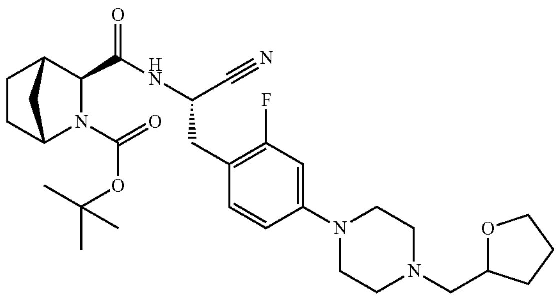
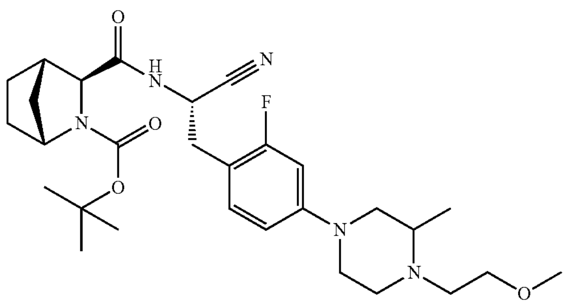
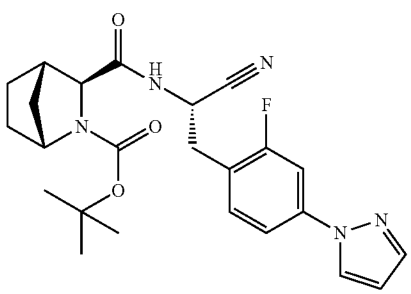
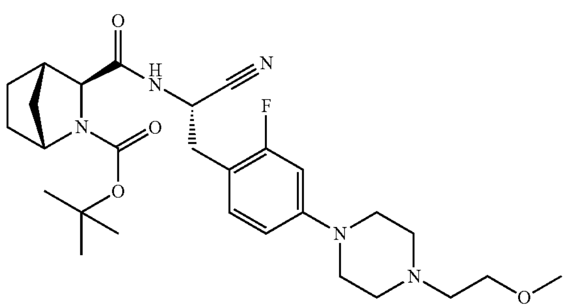
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.9	I-3.1.2		550	1.11	V011_S01
I-3.2.14	I-3.1.2		556	1.20	V011_S01
I-3.2.19	I-3.1.2		544	1.22	V011_S01
I-3.2.20	I-3.1.2		354 (M + H − BOC)+	1.20	V011_S01
I-3.2.22	I-3.1.2		530	1.13	V011_S01

TABLE 14-continued

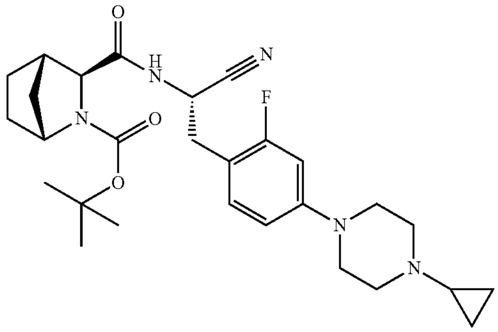
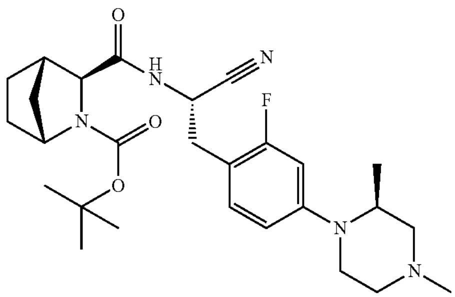
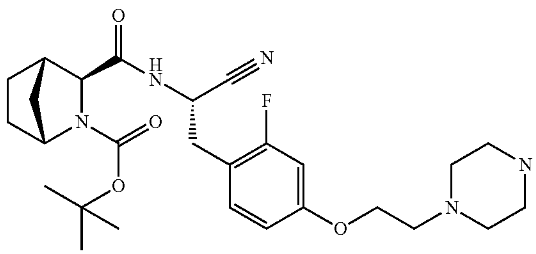
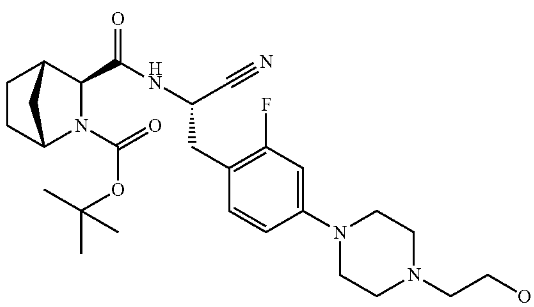
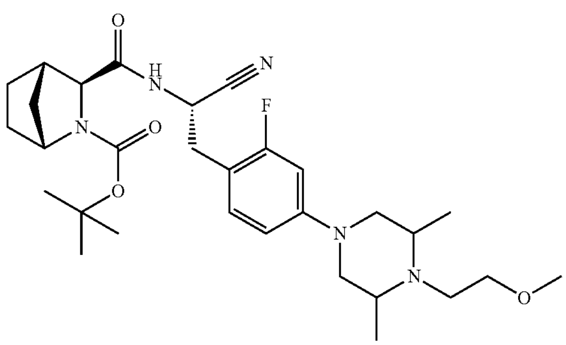
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.24	I-3.1.2		512	1.28	V011_S01
I-3.2.25	I-3.1.2		500	1.21	V011_S01
I-3.2.26 (forms together with I-3.2.27)	I-3.1.2		516	1.02	V011_S01
I-3.2.27 (forms together with I-3.2.26)	I-3.1.2		516	1.02	V011_S01
I-3.2.28;	I-3.1.2		558	1.25	V011_S01

TABLE 14-continued

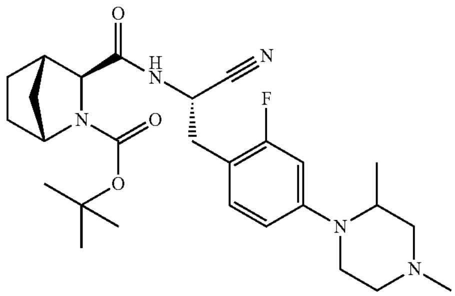
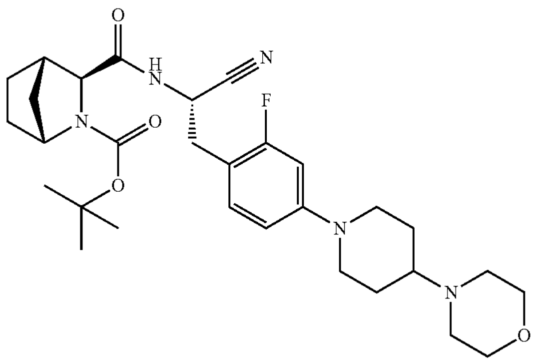
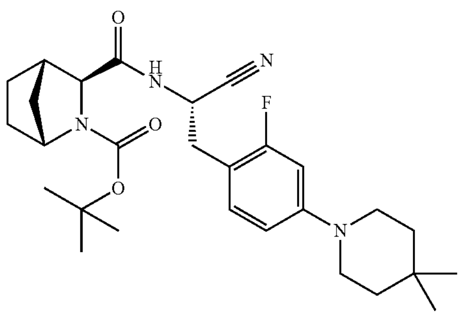
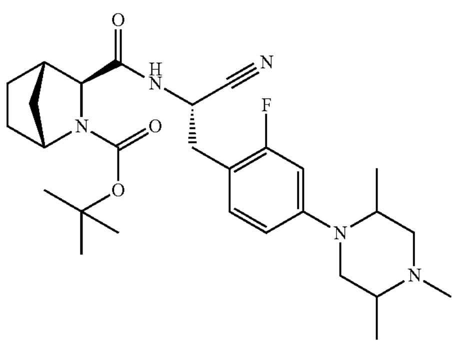
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.29	I-3.1.2		500	1.21	V011_S01
I-3.2.30	I-3.1.2		556	1.13	V011_S01
I-3.2.31	I-3.1.2		499	1.49	V011_S01
I-3.2.32;	I-3.1.2		514	1.21	V011_S01

TABLE 14-continued

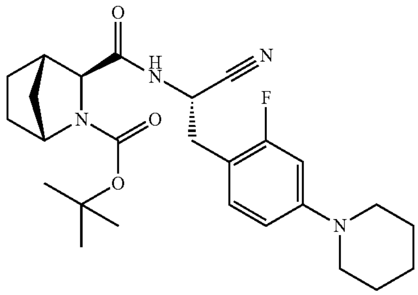
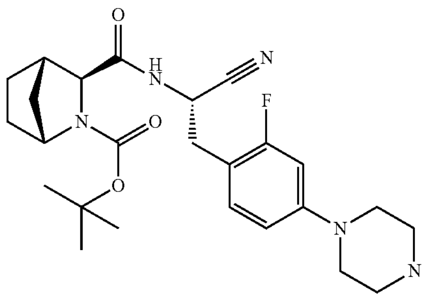
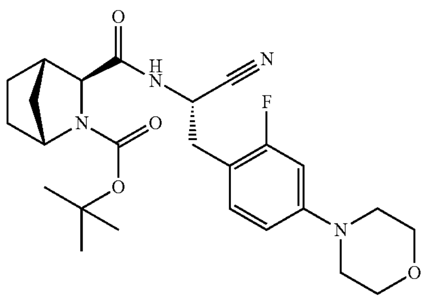
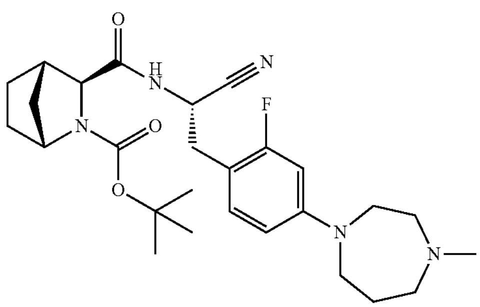
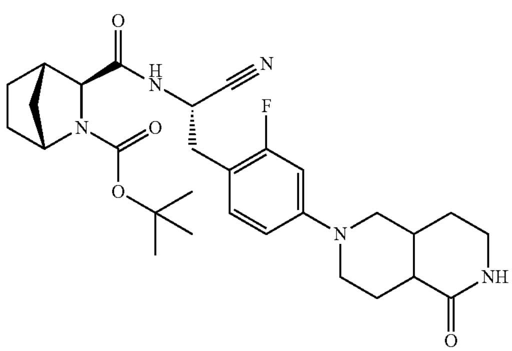
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.33	I-3.1.2		471	1.39	V011_S01
I-3.2.34	I-3.1.2		472	1.36	V011_S01
I-3.2.35	I-3.1.2		473	1.17	V011_S011
I-3.2.92	I-3.1.2		n.d.	0.67	X011_S03
I-3.2.93;	I-3.1.2		540	1.09	V011_S01

TABLE 14-continued

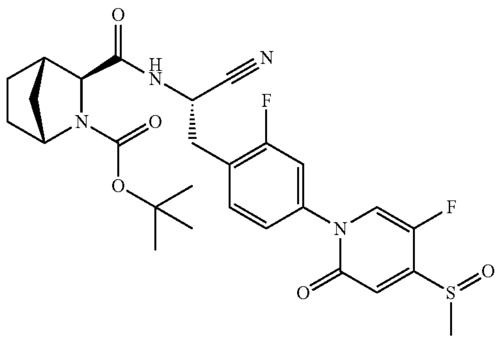
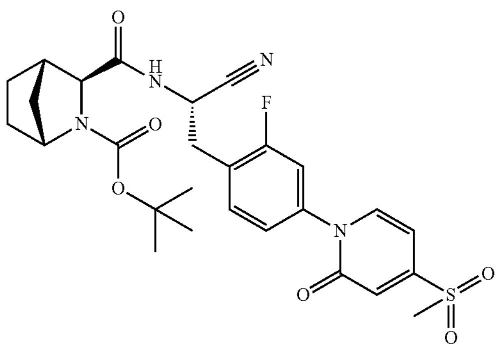
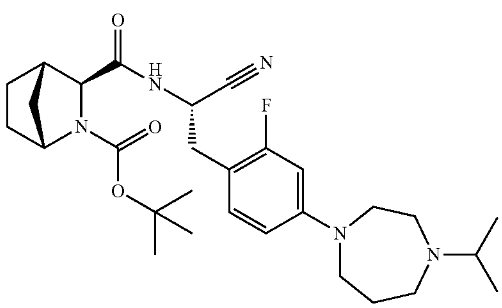
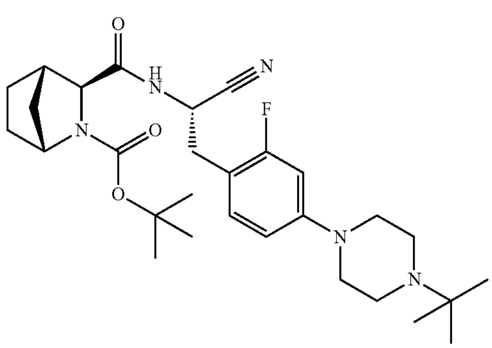
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.94	I-3.1.2		561	1.07	V011_S01
I-3.2.95	I-3.1.2		559	1.08	V011_S01
I-3.2.96	I-3.1.2		528	0.78	X011_S03
I-3.2.97	I-3.1.2		528	0.77	X011_S03

TABLE 14-continued

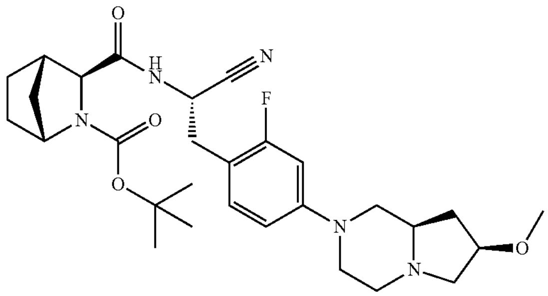
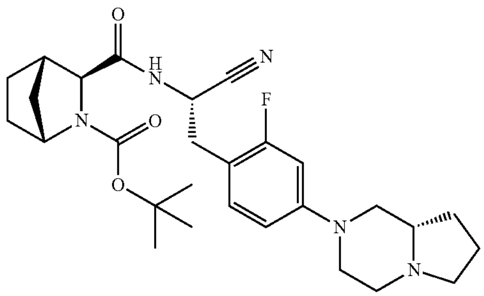
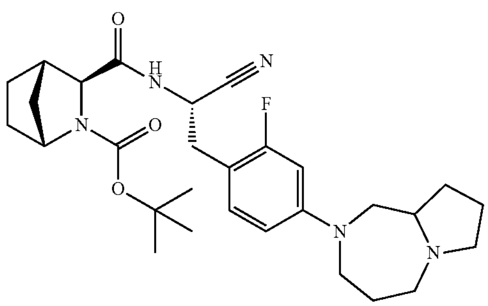
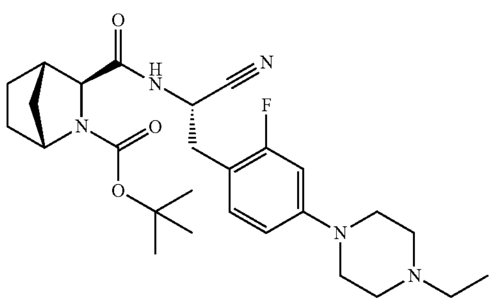
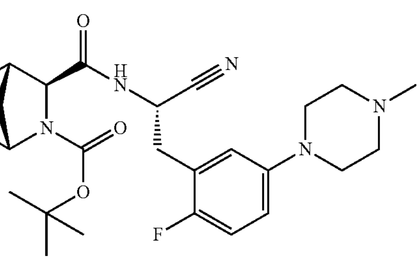
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.98	I-3.1.7		542	1.26	V011_S01
I-3.2.99	I-3.1.7		512	1.26	V011_S01
I-3.2.100	I-3.1.7		526	0.72	X011_S03
I-3.2.101	I-3.1.7		500	1.24	V011_S01
I-3.2.102	I-3.1.4		486	1.13	V011_S01

TABLE 14-continued

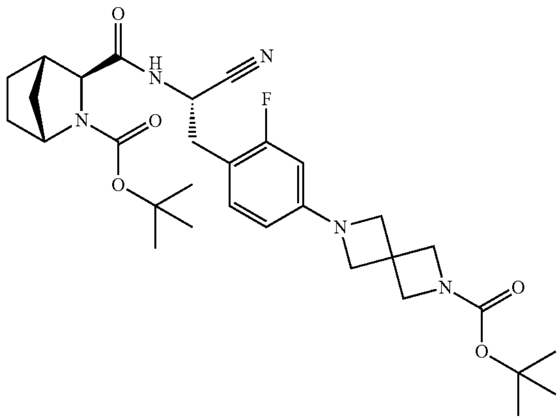
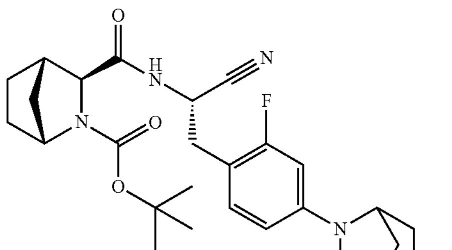
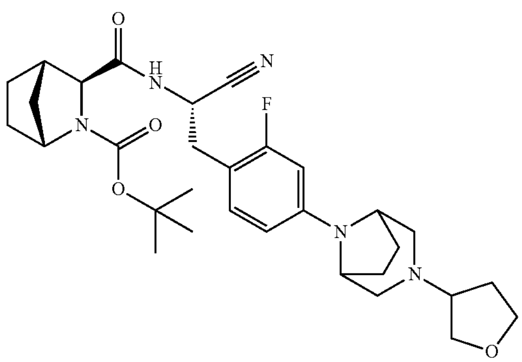
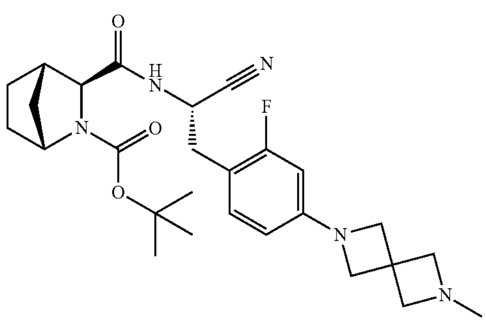
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.103	I-3.1.2		584	1.36	V011_S01
I-3.2.104	I-3.1.7		512	1.31	V011_S01
I-3.2.105	I-3.1.7		568	0.75	X011_S03
I-3.2.106	I-3.1.7		498	1.20	V011_S01

TABLE 14-continued

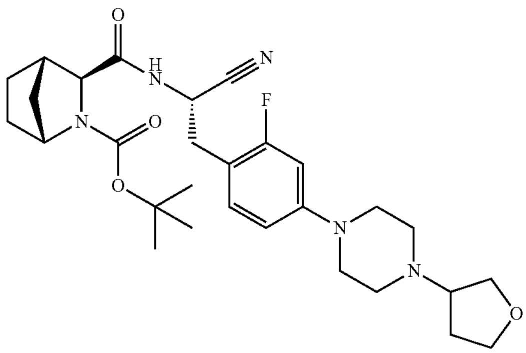
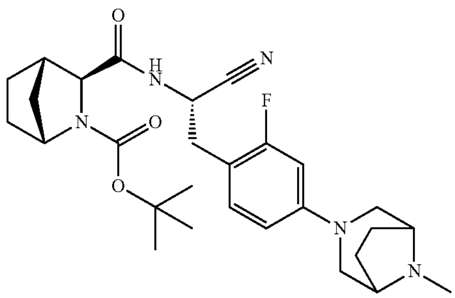
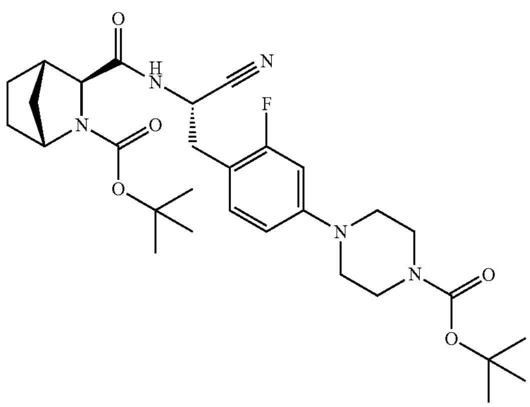
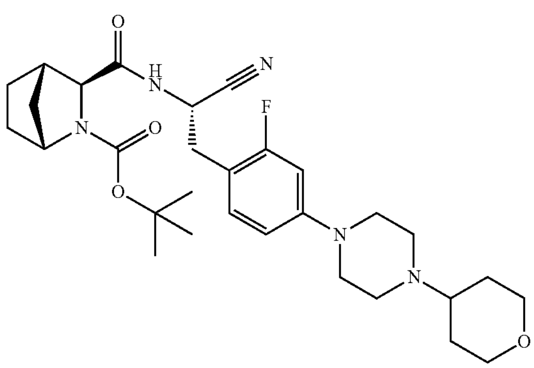
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.107	I-3.1.7		542	1.13	V011_S01
I-3.2.108	I-3.1.7		512	1.29	V011_S01
I-3.2.109	I-3.1.2		572	1.36	V011_S01
I-3.2.110	I-3.1.2		556	0.65	X011_S03

TABLE 14-continued

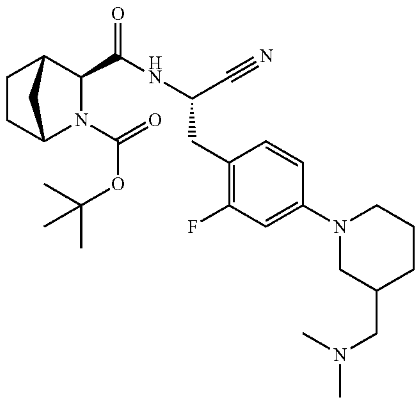
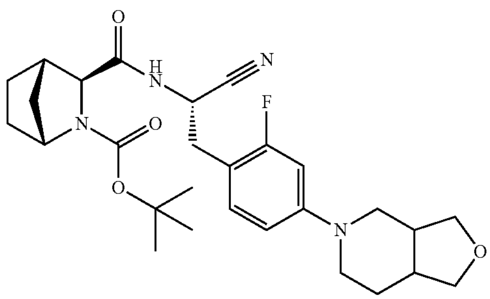
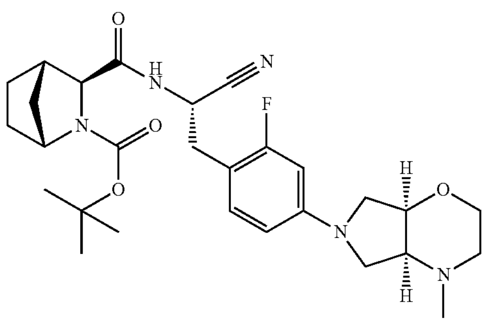
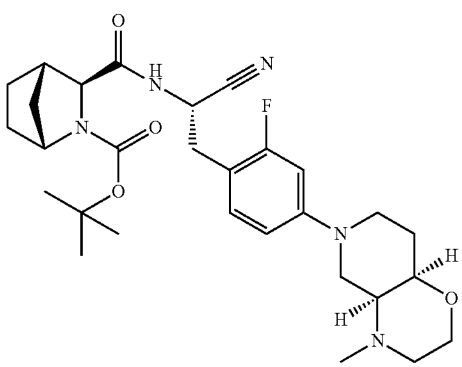
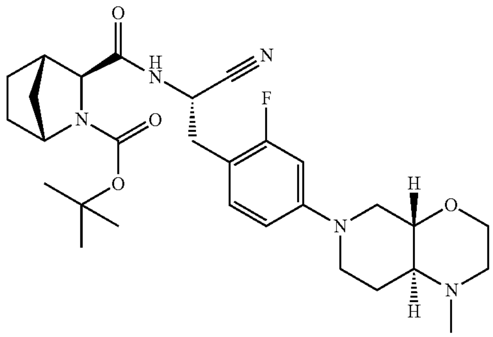
Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.111	I-3.1.1		528	0.79	X011_S03
I-3.2.112	I-3.1.7		513	0.69	X011_S03
I-3.2.114	I-3.1.7		n.d.	n.d.	n.d.
I-3.2.115	I-3.1.7		542	0.99	Z011_S03

TABLE 14-continued

Intermediate	Educt	Structure of Intermediates	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.116	I-3.1.7		542	1.017	Z011_S03

For the synthesis of the intermediates I-3.2.117 and I-3.2.118 to the educt I-3.1.2 with the appropriate amine in MeOH 0.14 eq copper(I)oxide is added (as shown in Table 15).

TABLE 15

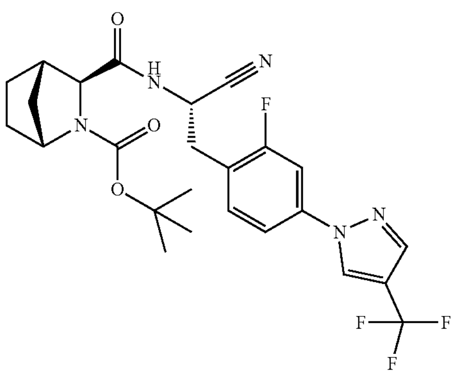
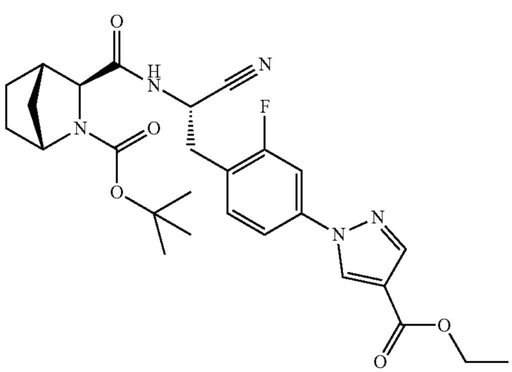
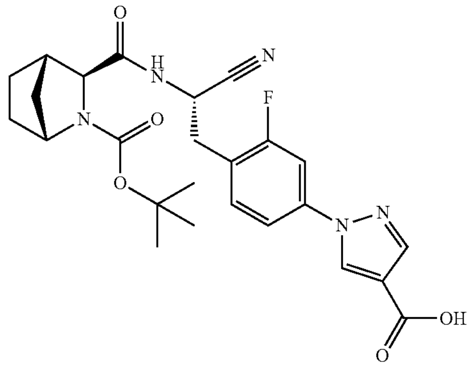
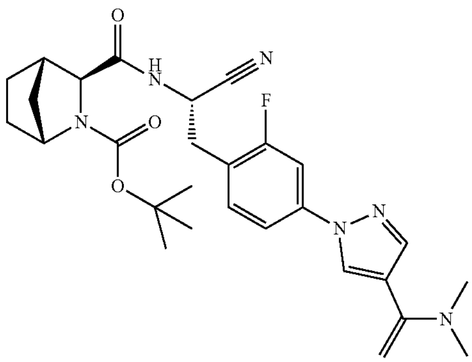
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.117	I-3.1.2		422 (M + H − BOC)+	1.32	V011_S01
I-3.2.118	I-3.1.2		526	1.28	V011_S01

TABLE 15-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.119	I-3.2.118		498	1.84	I_OJH_10_MEOH_DEA.M
I-3.2.120	I-3.2.119		525	1.10.	V011_S01

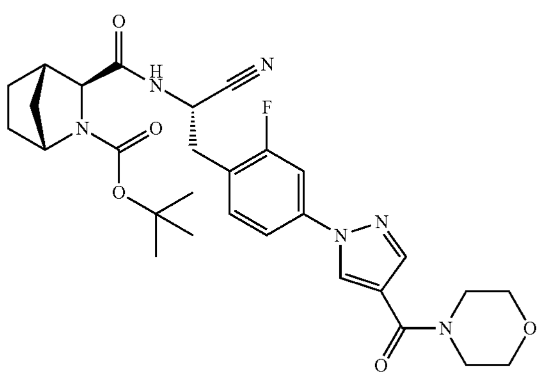
The synthesis of I-3.2.119 proceeds in the following way: I-3.2.118 (785 mg, 1.49 mmol) is dissolved in THF. LiOH (1.5 eq.) as aq. solution is added and stirred at r.t. for 9 h. The product mixture is acidified with 1 M HCl to pH 5 and purified by HPLC-MS. Yield: 61%.

The amide coupling for synthesis of intermediate I-3.2.120 proceeds in the following way: I-3.2.119 (40 mg, 0.08 mmol) HATU (33.6 mg, 0.088 mmol) and DIPEA (55.3 μL, 0.322 mmol) are dissolved in DMF. The mixture is stirred at r.t. for 15 min. Dimethylamine (120.6 μL, 0.241 mmol) is added, and the reaction mixture is stirred at r.t. for 1.5 h. The product mixture is separated by HPLC-MS.

The fractions are combined and freeze-dried. Yield: 85%.

The following intermediate as shown in Table 16 is synthesized in a similar fashion from the appropriate intermediate

TABLE 16

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.121	I-3.2.119		567	1.10	V011_S01

The reaction conditions for I-3.2.94 and I-3.2.95 differ: Pyridine instead of TEA is used.

The reaction conditions are 80° C. overnight.

The reaction conditions for I-3.2.111 differ: 2 eq of N-Methylmorpholine N-Oxid is added to the reaction.

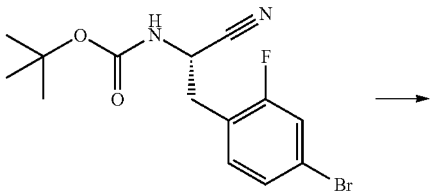
Step 2: Synthesis of Example 32

To I-3.2.4 (82 mg, 0.15 mmol) in acetonitrile, p-toluenesulfonic acid monohydrate (95 mg, 0.50 mmol) is added and stirred overnight at r.t. The reaction mixture is basified with ammonium solution. 0.5 mL water and 1 mL ACN are added. The precipitate is filtered off, washed with ACN and dried. The crude product is triturated with aq. sodium hydrogencarbonate solution, filtered by suction and dried. Yield 31%, m/z 448 [M+H]+, rt 1.28 min, LC-MS Method V011_S01.

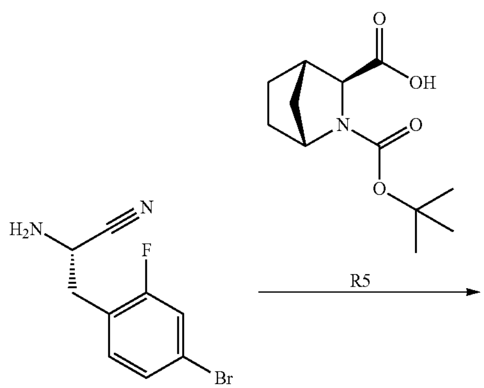
Method A3

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-(3-methylsulfonylphenyl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

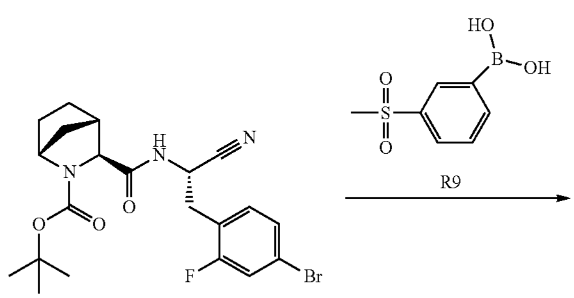
Example 4



I-1.1

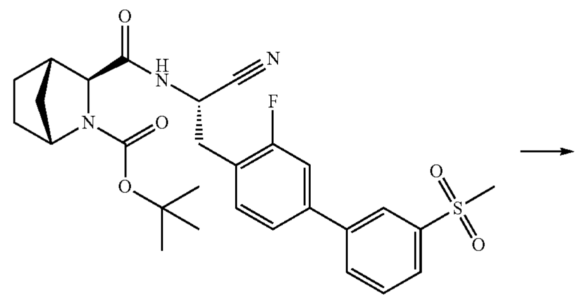


I-4.1

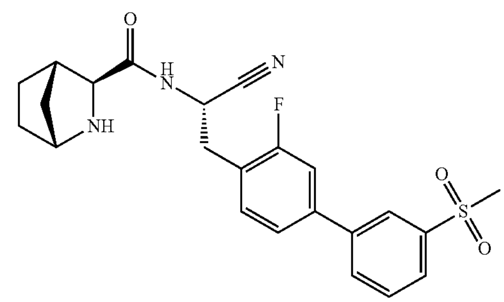


I-2.2

-continued



I-4.3



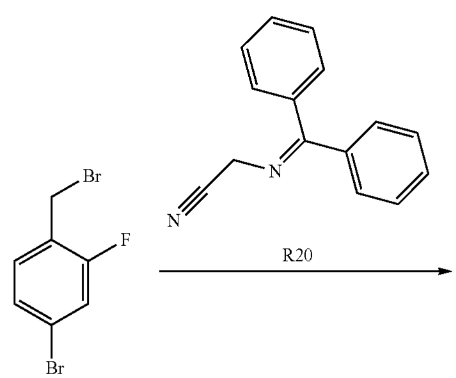
Example 4

Step 1: Synthesis of Intermediate I-4.1

To I-1.1 (5.00 g, 14 mmol) in acetonitrile (250 mL) p-toluenesulfonic acid monohydrate (3.05 g, 16 mmol) is added and the mixture is stirred for 3 d. The precipitate is filtered off and the solution is washed with acetonitrile. The residue is stirred with aq. NaHCO3 solution (2%), and extracted with ethyl acetate. The organic layer is dried over $MgSO_4$ and concentrated. Yield 78%, m/z 243/245 [M+H]+, rt 0.76 min, LC-MS Method V018_S01.

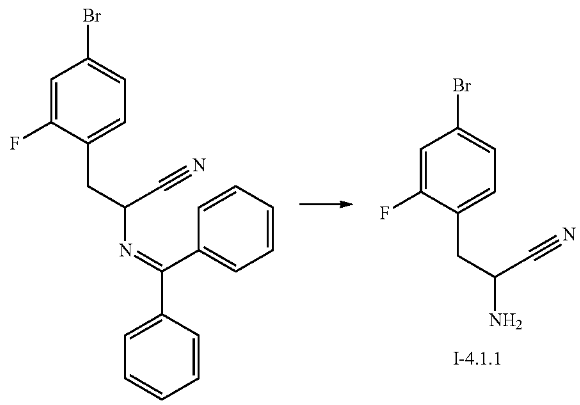
The further intermediates belong to the following description

Synthesis of 2-amino-3-(4-bromo-2-fluoro-phenyl)propanenitrile



R19

-continued



I-4.0 I-4.1.1

Step 1.1: Synthesis of Intermediate I-4.0 (Compare with Synthesis of Intermediate I-7.1)

To R19 (28.1 g, 104 mmol) and R20 (21.0 g, 95 mmol) in DCM (130 mL) benzyltrimethylammonium chloride (1.77 g, 9.5 mmol) is added. Under strong stirring water (8 mL) and aq. NaOH solution (19 mol/L, 9 mL) are added (exothermic reaction). The reaction mixture is stirred for 12 h. Water is added and the product is extracted with DCM. The organic layer is dried over $MgSO_4$ and concentrated. The crude product is used in step 2. Yield >95%, rt 1.56 min, LC-MS Method V003__003.

The following intermediates as shown in Table 20 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 20

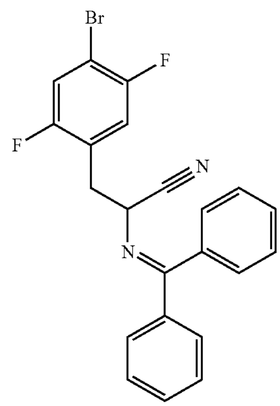
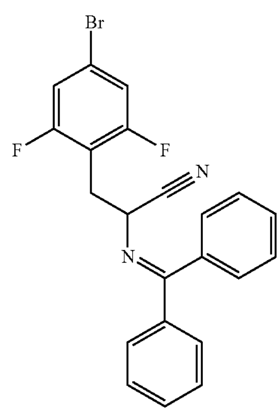
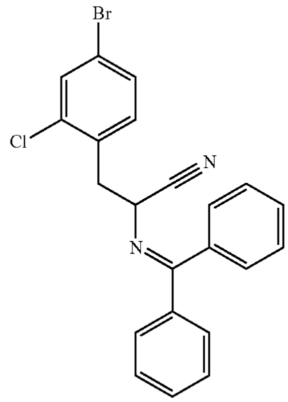
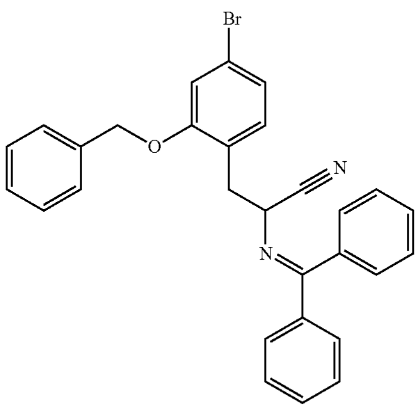
Intermediate	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.0.1		n.d.	n.d.	n.d.
I-4.0.2		425/427	1.51	V011_S01

TABLE 20-continued

Intermediate	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.0.3		n.d.	n.d.	n.d.
I-4.0.4		495/497	0.96	X018_S01

Step 1.2: Synthesis of Intermediate I-4.1.1 (Compare with Synthesis of Intermediate I-7.2)

To I-4.0 (40.8 g, 100 mmol) in dioxane (400 mL) hydrogen chloride solution in dioxane (4 mol/L, 27.5 mL, 9.5 mmol) is added. The reaction mixture is stirred for 12 h. Aq. hydrochloric acid (1 mol/L, 100 mL) is added and the mixture is stirred for additional 2 h. The reaction is concentrated, the residue is stirred with acetonitrile and the precipitate is filtered off. Yield 49%, m/z 243 [M+H]+, rt 0.42 min, LC-MS Method X001__004.

The following intermediates as shown in Table 21 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 21

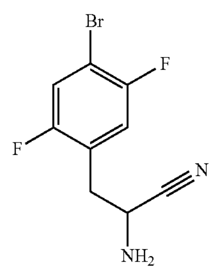
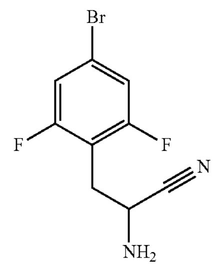
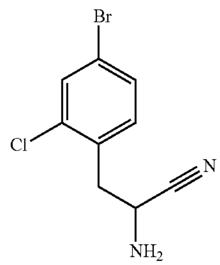
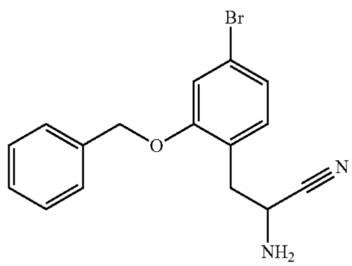
Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-4.1.1.1	I-4.0.1		261	0.35	Z001_002

TABLE 21-continued

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-4.1.1.2	I-4.0.2		261/263	0.34	V012_S01
I-4.1.1.3	I-4.0.3		259	0.39	X001_004
I-4.1.1.4	I-4.0.4		331/333	0.48	V018_S01

Step 2: Synthesis of Intermediate I-2.2

To R5 (2.82 g, 11 mmol) in dry DCM (150 mL) diisopropylethylamine (5.8 mL, 33 mmol) and HATU (5.1 g, 13 mmol) are added and the mixture is stirred for 30 min. Then a solution of I-4.1 (2.75 g, 11 mmol) in DCM (50 mL) is added and stirred for 12 h. The mixture is washed with water, aq. K2CO3 solution (5%) and 1 M HCl. The organic layer is dried over $MgSO_4$ and concentrated. Yield 68%, m/z 466/468 [M+H]+, rt 1.25 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 22 are synthesized in a similar fashion from the appropriate intermediate: ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group)

TABLE 22

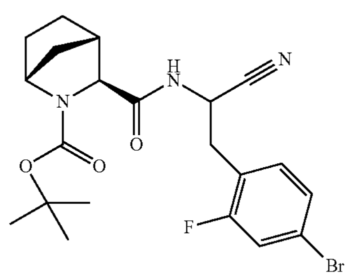
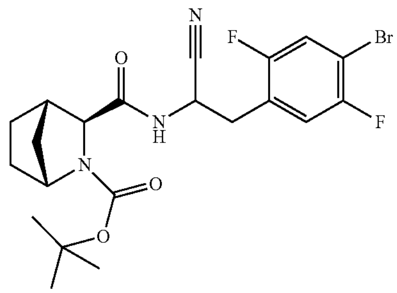
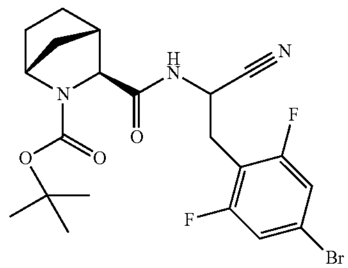
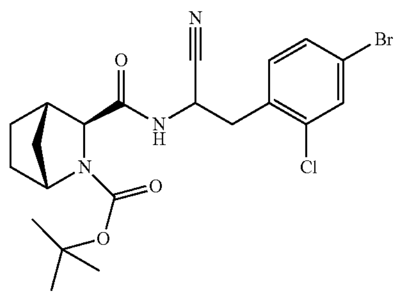
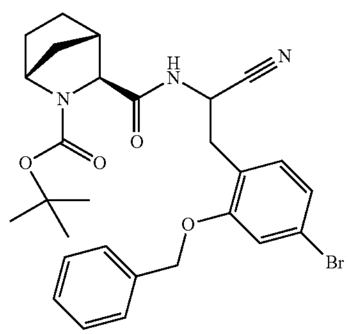
Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-4.2.1	I-4.1.1		466	0.78	X001_004

TABLE 22-continued

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-4.2.2	I-4.1.1.1		484	1.29	V011_S01
I-4.2.3	I-4.1.1.2		484/486	1.29	V011_S01
I-4.2.4	I-4.1.1.3		n.d.	n.d.	n.d.
I-4.2.5	I.4.1.1.4		554	1.42	V011_S01

Step 3: Synthesis of Intermediate I-4.3

To I-2.2 (300 mg, 0.64 mmol) in acetonitrile (7.5 mL) R9 (142 mg, 0.71 mmol) is added. The mixture is purged with argon 1,1-Bis(di-tert-butylphosphino)ferrocene palladium dichloride (42 mg, 0.10 mmol) and aq. sodium carbonate solution (2 mol/L, 0.64 mL) are added and heated to 70° C. for 2.5 h. Ethyl acetate and water are added to the reaction mixture. The organic layer is washed with aq. NaHCO3 solution (5%) and water. The organic layer is dried over $MgSO_4$ and concentrated. Yield raw product >95% m/z 442 [M+H]+, rt 0.93 min, LC-MS Method Z018_S04.

The following intermediates as shown in Table 23 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 23

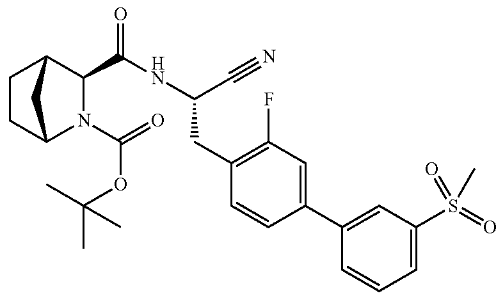
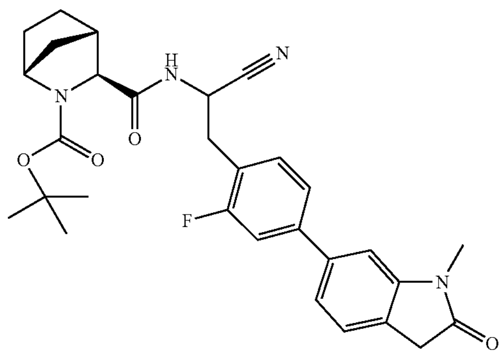
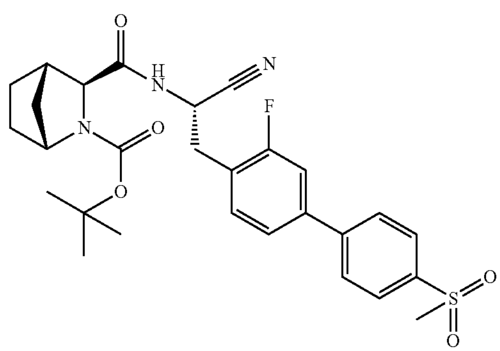
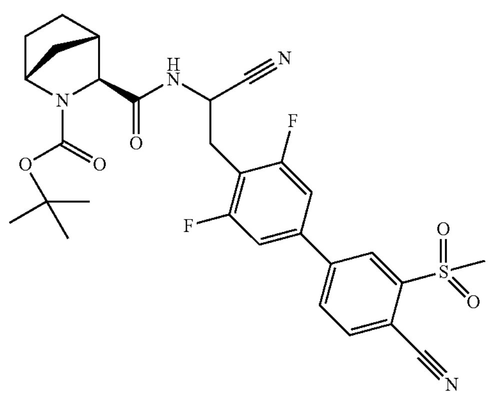
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.1	I-4.2.1		567	1.19	V011_S01
I-4.3.2	I-4.2.1		533	0.75	X001_004
I-4.3.3	I-2.2		442	0.92	Z018_S04
I-4.3.4	I-4.2.3		585	1.20	V011_S01

TABLE 23-continued

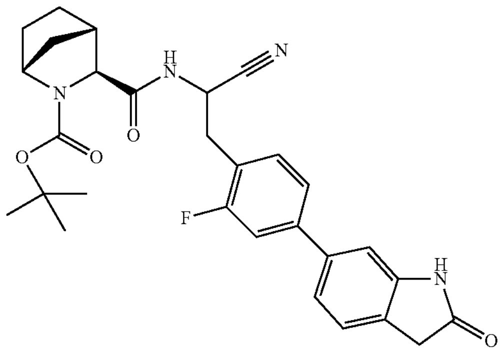
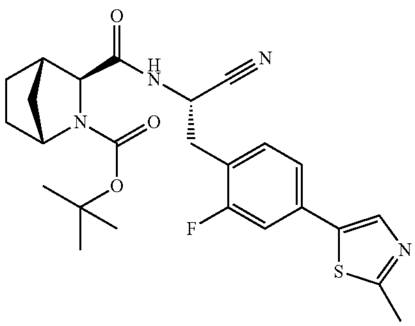
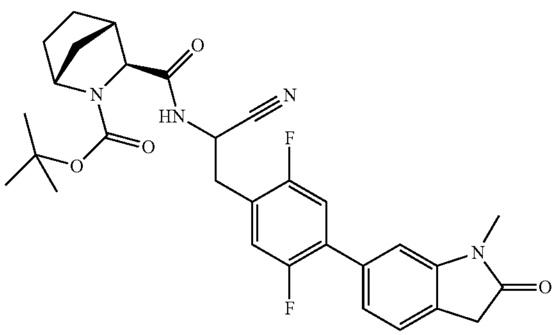
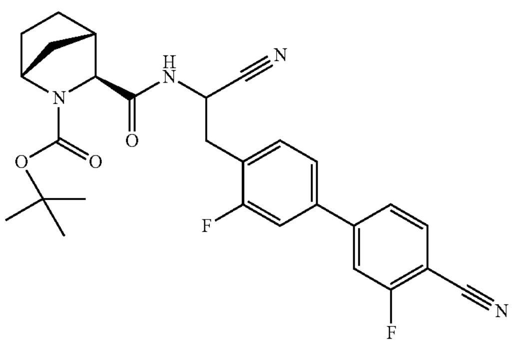
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.5	I-4.2.1		519	0.62	Z001_002
I-4.3.6	1-2.2		429	0.95	Z018_S04
I-4.3.8	I-4.2.2		551	1.22	V011_S01
I-4.3.9	I-4.2.1		n.d.	1.39	V003_003

TABLE 23-continued

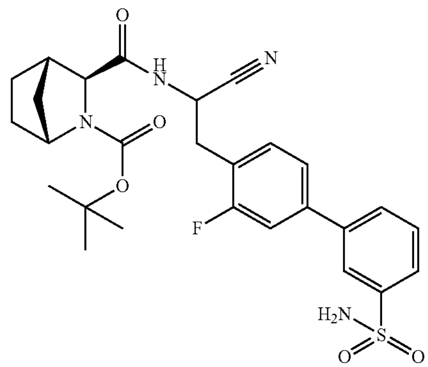
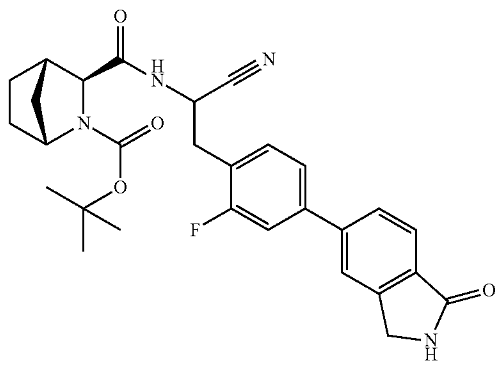
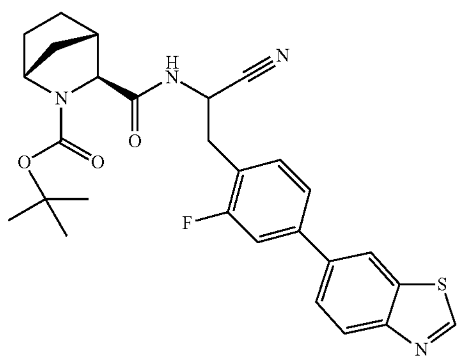
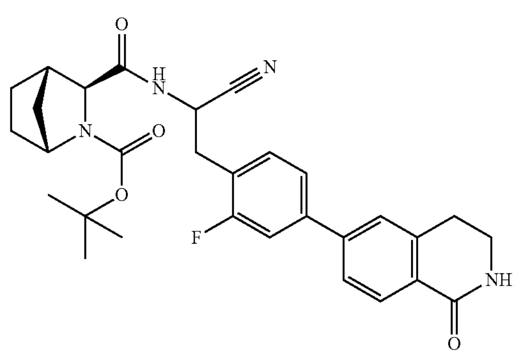
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.10	I-4.2.1		543	0.57	001_CA07
I-4.3.11	I-4.2.1		518	0.55	001_CA07
I-4.3.12	I-4.2.1		n.d.	n.d.	n.d.
I-4.3.13	I-4.2.1		532	0.57	001_CA07

TABLE 23-continued

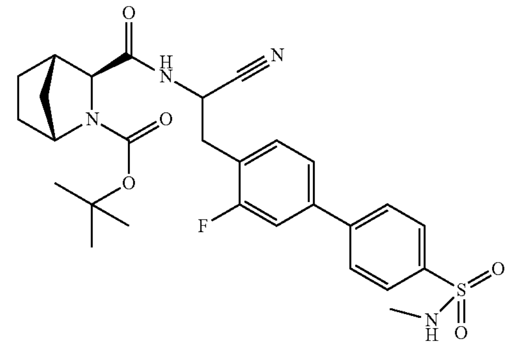
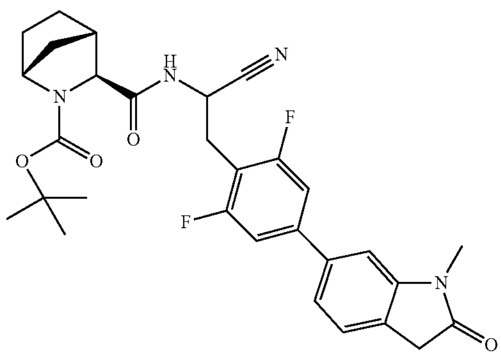
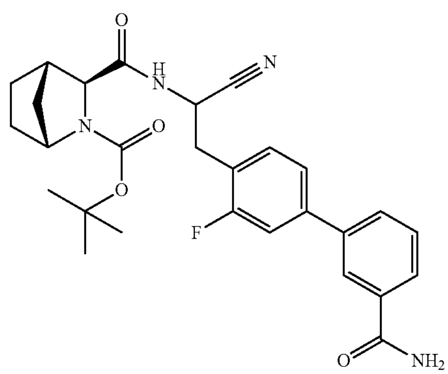
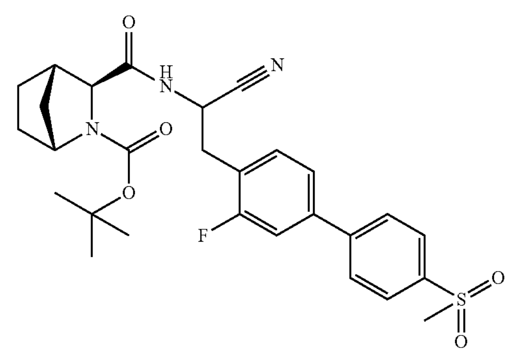
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.14	I-4.2.1		556	0.60	001_CA07
I-4.3.15	I-4.2.3		551	1.21	V011_S01
I-4.3.16	I-4.2.1		506	0.56	001_CA07
I-4.3.17	I-4.2.1		541	0.60	001_CA07

TABLE 23-continued

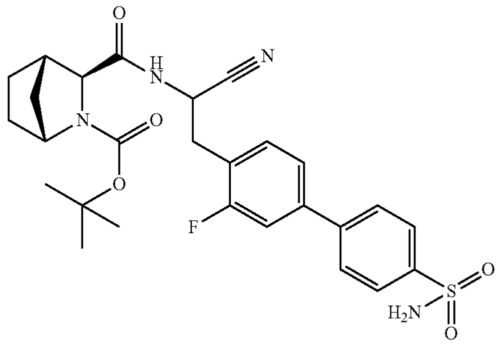
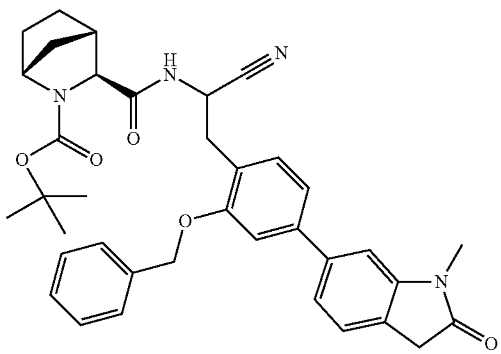
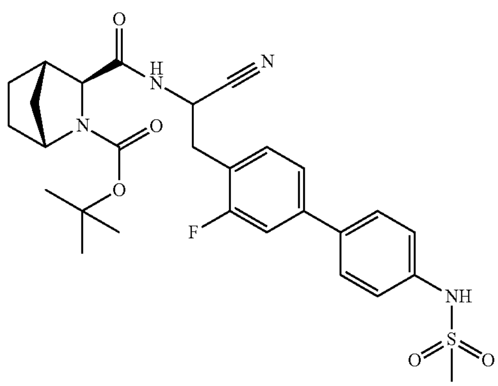
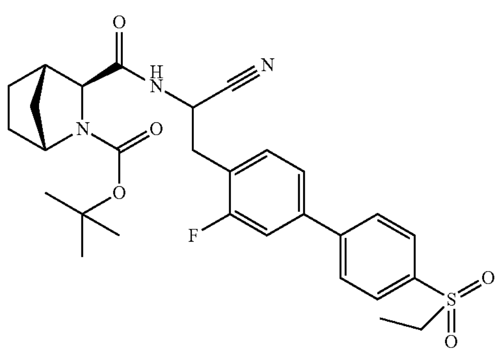
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.18	I-4.2.1		542	0.56	001_CA07
I-4.3.19	I-4.2.5		621	1.33	V011_S01
I-4.3.20	I-4.2.1		556	0.60	001__CA07
I.4.3.21	I-4.2.1		556	0.62	001_CA07

TABLE 23-continued

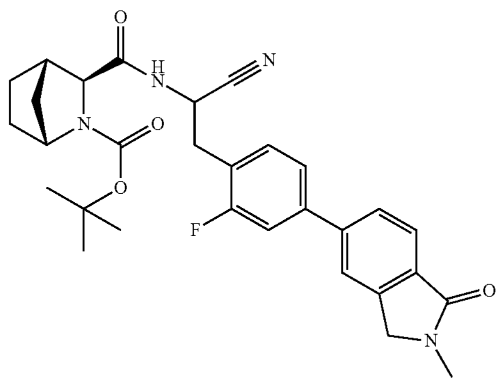
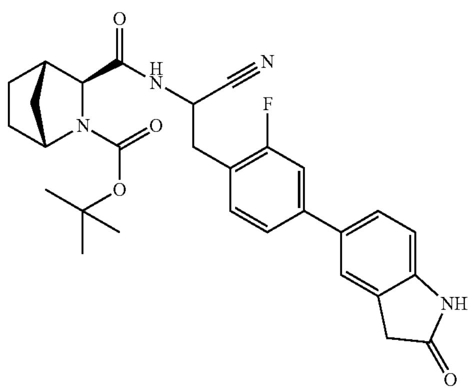
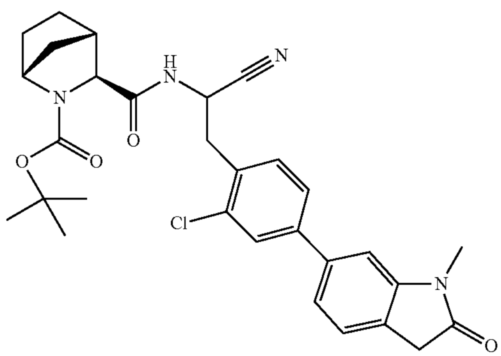
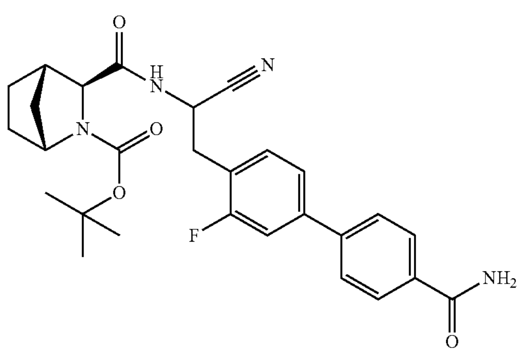
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.22	I-4.2.1		532	0.58	001_CA07
I-4.3.23	I-4.2.1		n.d.	1.22	Z018_S04
I-4.3.24	I-4.2.4		n.d.	n.d.	n.d.
I-4.3.25	I-4.2.1		506	0.55	001_CA07

TABLE 23-continued

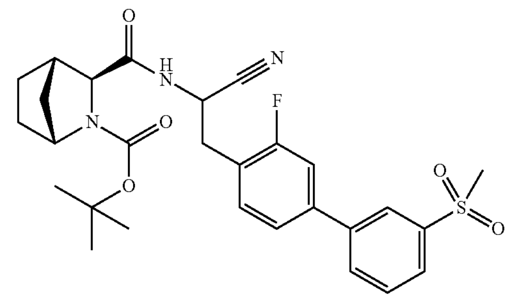
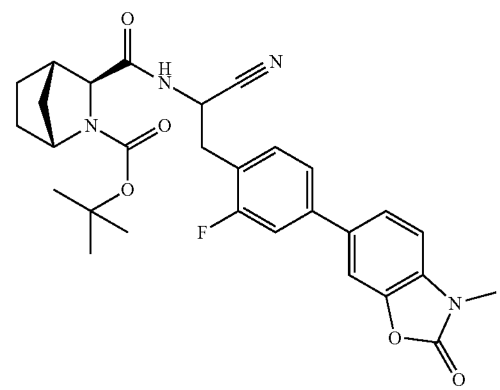
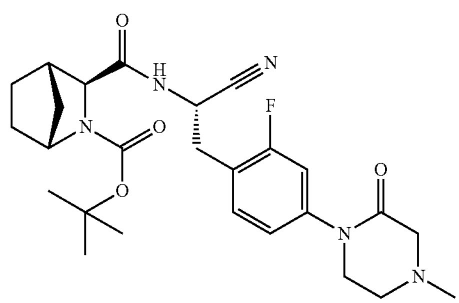
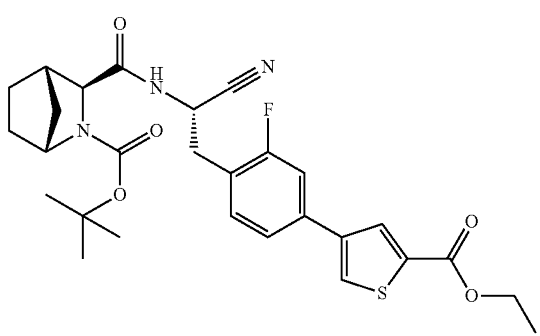
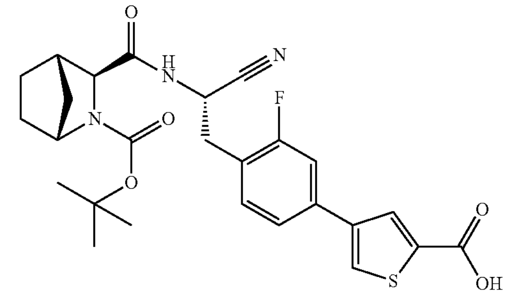
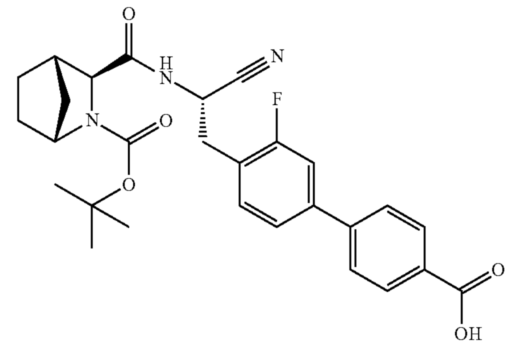
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.26	I-4.2.1		n.d.	n.d.	n.d.
I-4.3.27	I-4.2.1		534	0.63	001_CA07
I-4.3.28	I-2.2		500	0.98	V011_S01
I-4.3.29	I-2.2		442 (M + H − BOC)+	1.09	Z018_S04

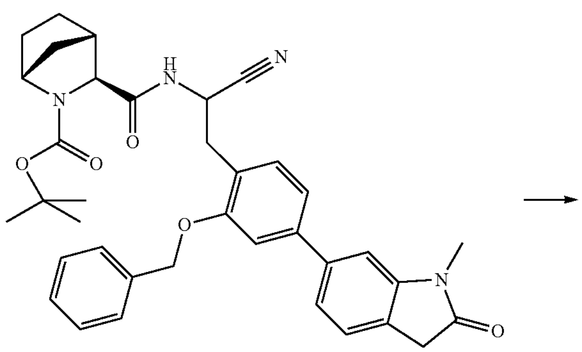
TABLE 23-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.30	I-4.3.29		414 (M + H − BOC)+	0.60	Z011_S03
I-4.3.31	I-2.2		408 (M + H − BOC)+	0.93	Z018_S04

The reaction conditions for I-4.3.28 differ: Under argon atmosphere I-2.2 (250 mg, 0.54 mmol), potassium carbonate (150 mg, 1.07 mmol), copper (I) iodide (10 mg, 0.05 mmol), N,N'-dimethylethylendiamine (25 μL, 0.23 mmol) and 4-methyl-piperazin-2-one (75 mg, 0.66 mmol) in dioxane (10 mL) are heated to 80° C. for 8 d. The reaction mixture is filtered and the solution is concentrated. The residue is purified by reversed phase HPLC. Yield 30%, m/z 500 [M+H]+, rt 0.98 min, LC-MS Method V011_S01.

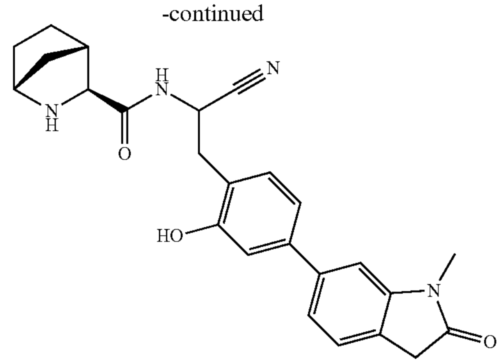
The synthesis of I-4.3.30 proceeds in the following way: I-4.3.29 (509 mg, 0.94 mmol) is dissolved in dioxane. LiOH (1.5 eq.) as aq. solution is added dropwise to the solution and stirred at r.t. for 8 h. The product mixture is extracted 2× with DCM. The organic layer is extracted twice with water. The water phase is acidified with 1 M HCl to pH 4, the solvent removed in vacuo to yield the crude product, which is purified by HPLC-MS (Gilson, mass flow 120 mL/min, 10 μM, 200 g Xbridge RP18, ACN/water/NH_3). Yield: 44%.

Intermediate I-4.3.19 is additionally treated with BBr_3 to give example 120:



I-4.3.19

-continued



example 120

I-4.3.19 (600 mg, 0.97 mmol) in DCM (50 mL) is stirred at −5° C. Then boron tribromide solution (1 mol/L in DCM, 2.90 mL) is added dropwise. The reaction mixture is stirred at 0° C. for 90 min and then stirred at room temperature for additional 12 h. The mixture is cooled down again to −5° C. and is quenched with conc. ammonia solution. The mixture is concentrated and purified by reversed phase HPLC. Yield 5%, m/z 429 [M+H]+, rt 0.81 min, LC-MS Method V018_S04.

Additional Step: Amide Coupling to Afford I-4.3.32

The amide coupling for synthesis of intermediate I-4.3.32 proceeds in the following way: I-4.3.30 (35 mg, 0.068 mmol) TBTU (45 mg, 0.14 mmol) and N-methylmorpholine (75 μL, 0.68 mmol) are dissolved in DMF. The mixture is stirred at r.t. for 5 min. 0.5 M ammonia in dioxane (2 mL, 1 mmol) is added, and the reaction mixture is stirred at r.t. for 12 h. The product mixture is separated by HPLC-MS (Waters, 30×100 mm, 10 μM, sunfire RP18, ACN/water/TFA). The fractions are combined and freeze-dried. Yield: 59%.

The following amide intermediates as shown in Table 24.1 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 24.1

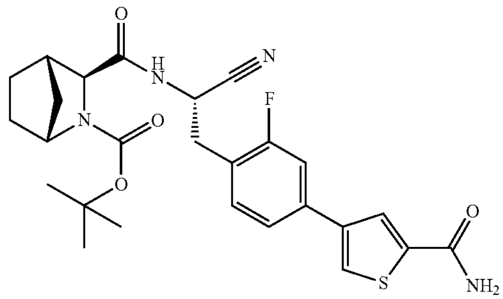
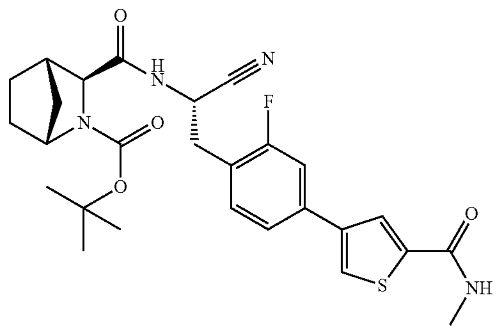
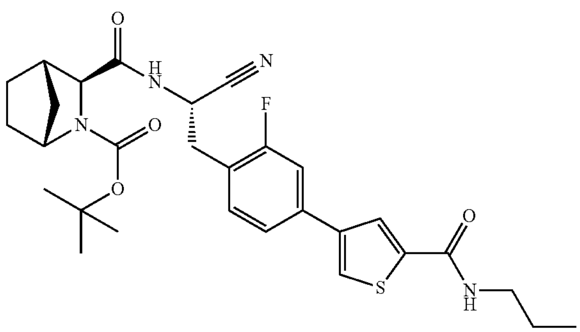
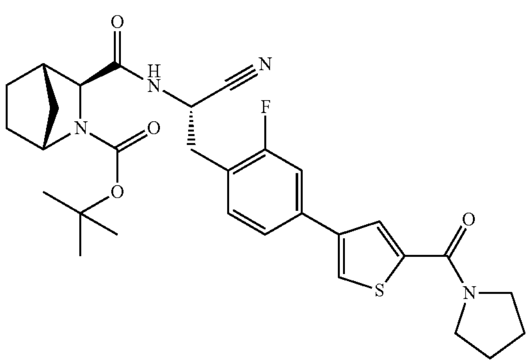
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.32	I-4.3.30		413 (M + H − BOC)+	0.89	Z018_S04
I-4.3.33	I-4.3.30		427 (M + H − BOC)+	0.92	Z018_S04
I-4.3.34	I-4.3.30		455 (M + H − BOC)+	1.00	Z018_S04
I-4.3.35	I-4.3.30		467 (M + H − BOC)+	0.99	Z018_S04

TABLE 24.1-continued

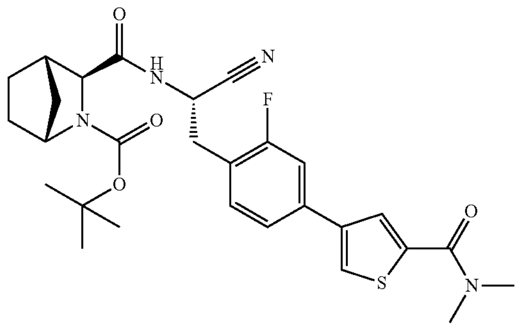
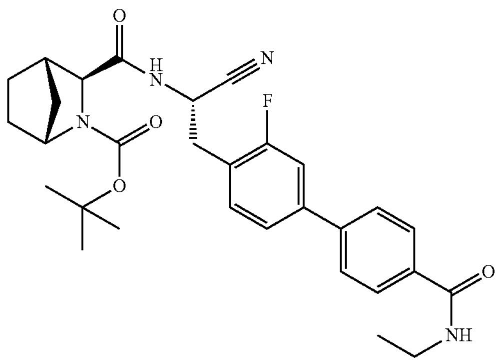
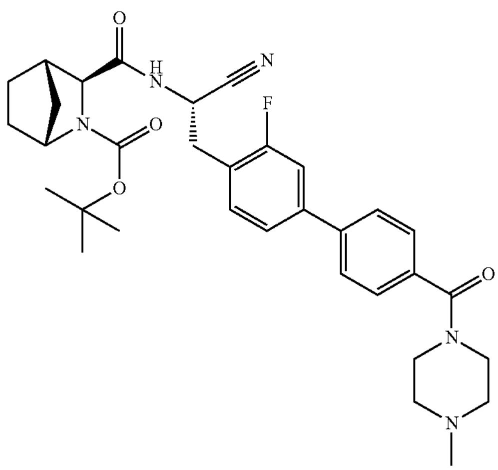
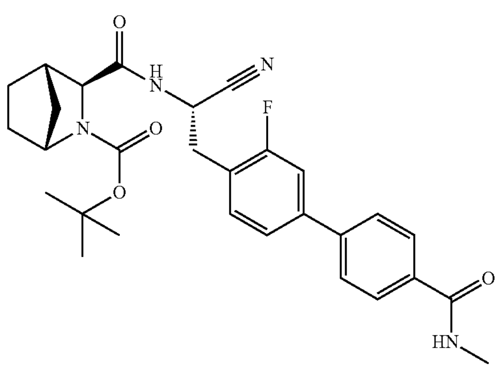
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.36	I-4.3.30		441 (M + H − BOC)+	0.95	Z018_S04
I-4.3.37	I-4.3.31		435 (M + H − BOC)+	0.95	Z018_S04
I-4.3.38	I-4.3.31		490 (M + H − BOC)+	0.75	Z018_S04
I-4.3.39	I-4.3.31		421 (M + H − BOC)+	0.91	Z018_S04

TABLE 24.1-continued

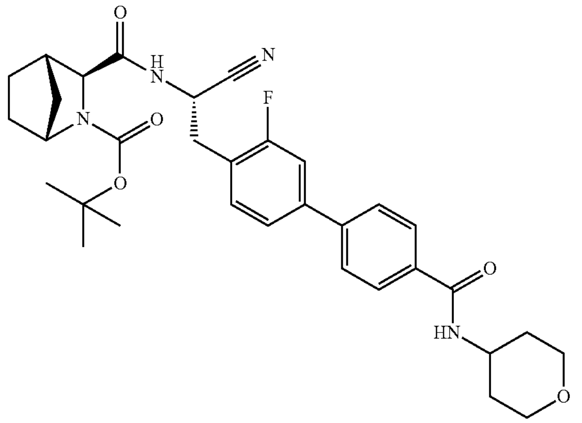
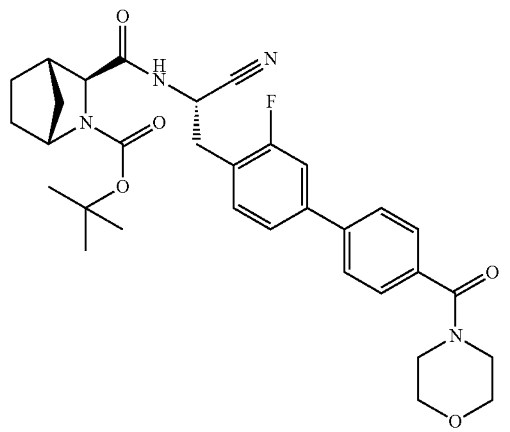
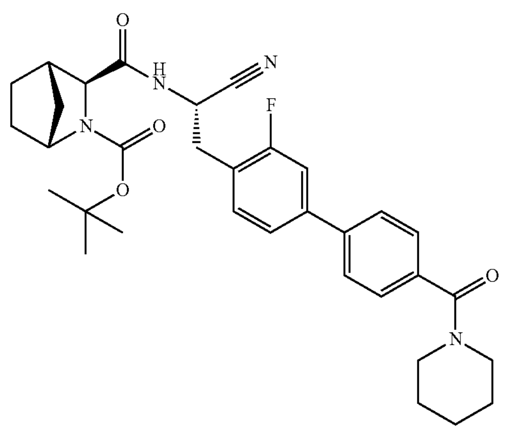
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.40	I-4.3.31		491 (M + H − BOC)+	0.94	Z018_S04
I-4.3.41	I-4.3.31		477 (M + H − BOC)+	0.93	Z018_S04
I-4.3.42	I-4.3.31		475 (M + H − BOC)+	1.02	Z018_S04

TABLE 24.1-continued

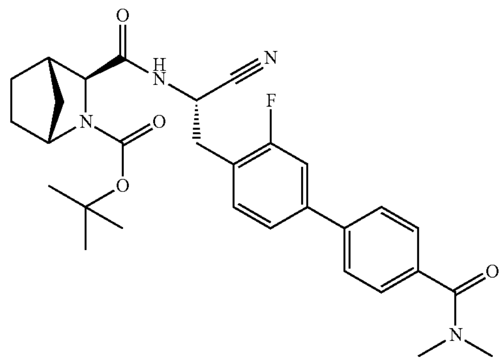
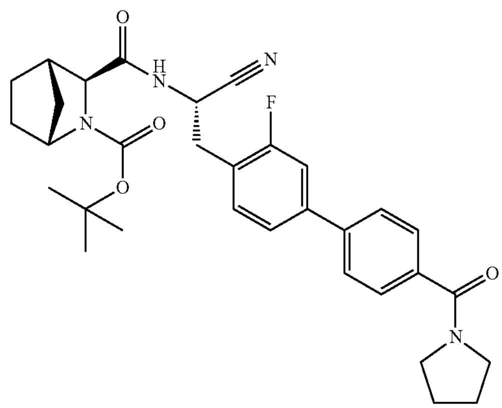
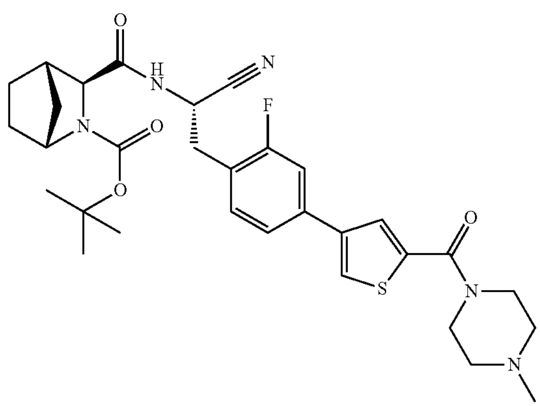
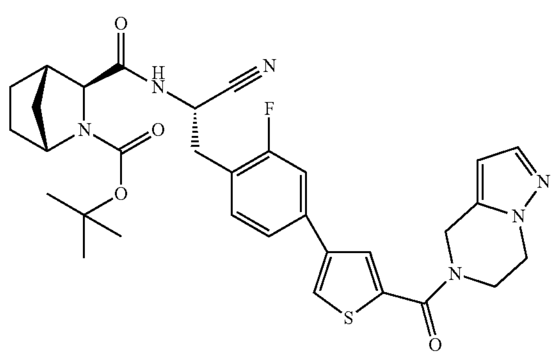
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.43	I-4.3.31		435 (M + H − BOC)+	0.94	Z018_S04
I-4.3.44	I-4.3.31		461 (M + H − BOC)+	0.97	Z018_S04
I-4.3.45	I-4.3.30		496 (M + H − BOC)+	0.89	Z011_S03
I-4.3.46	I-4.3.30		519 (M + H − BOC)+	0.90	Z018_S04

TABLE 24.1-continued

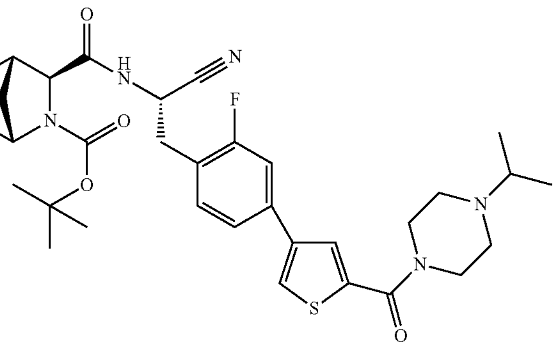
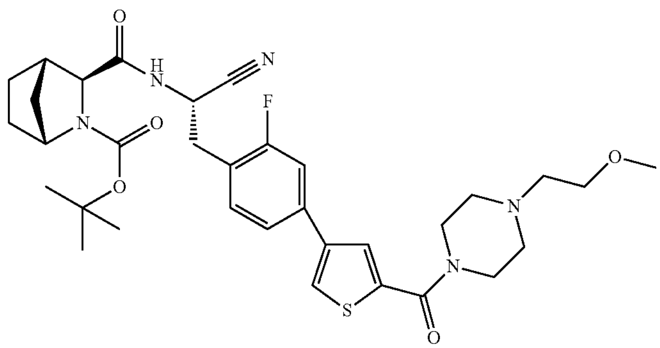
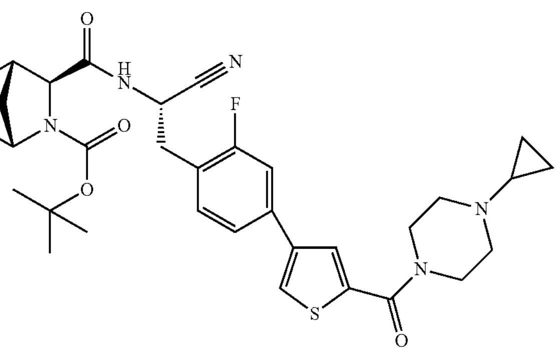
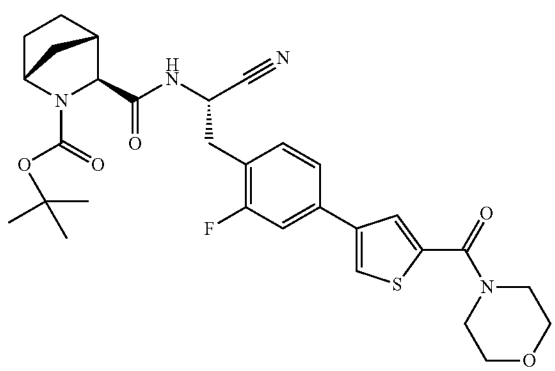
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.47	I-4.3.30		524 (M + H − BOC)+	0.97	Z011_S03
I-4.3.48	I-4.3.30		540 (M + H − BOC)+	0.91	Z011_S03
I-4.3.49	I-4.3.30		422 (M + H − BOC)+	0.98	Z011_S03
I-4.3.50	I-4.3.30		483 (M + H − BOC)+	0.90	Z011_S03

TABLE 24.1-continued

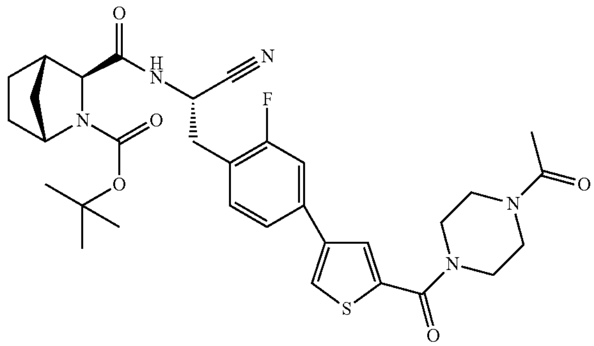
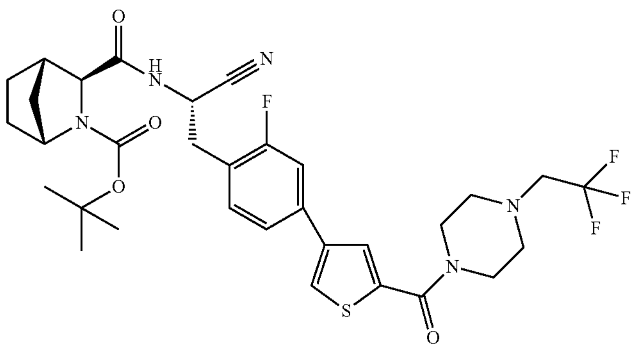
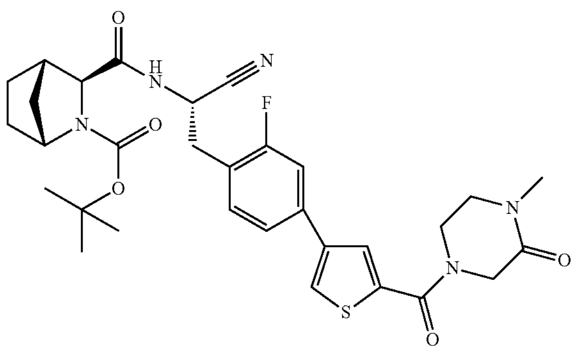
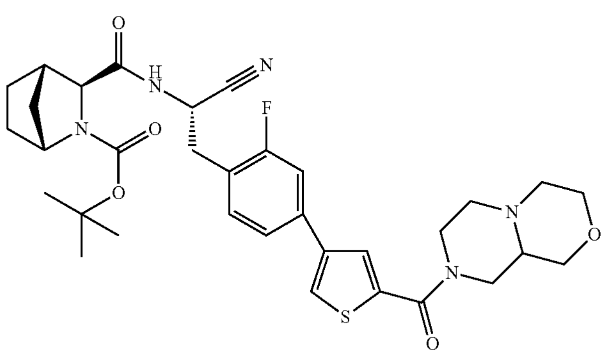
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.51	I-4.3.30		424 (M + H − BOC)+	0.86	Z011_S03
I-4.3.52	I-4.3.30		564 (M + H − BOC)+	0.98	Z018_S04
I-4.3.53	I-4.3.30		510 (M + H − BOC)+	0.85	Z011_S03
I-4.3.54	I-4.3.30		583 (M + H − BOC)+	0.89	Z011_S03

TABLE 24.1-continued

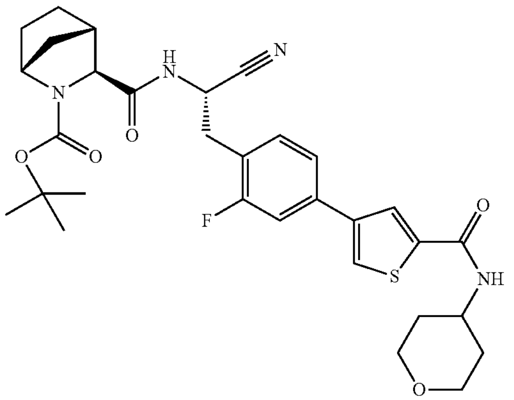
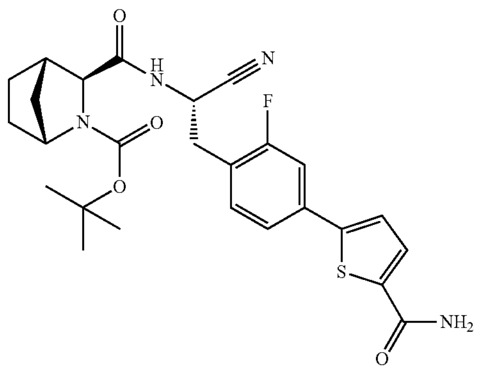
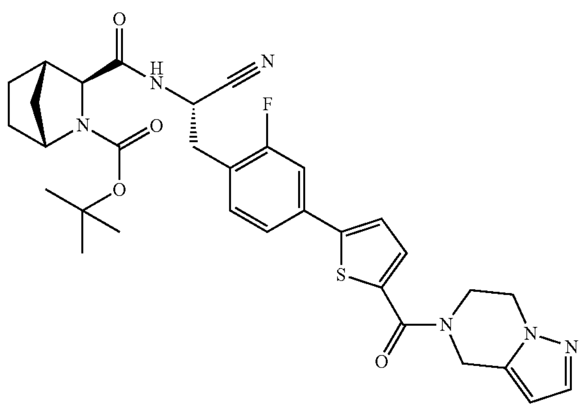
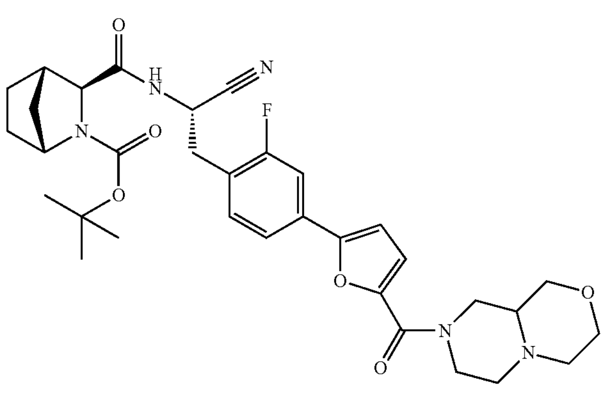
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.55	I-4.3.30		497 (M + H − BOC)+	0.91	Z011_S03
I-4.3.56	I-2.3.41		413 (M + H − BOC)+	0.84	Z011_S03
I-4.3.57	I-2.3.41		519 (M + H − BOC)+	0.94	Z018_S04
I-4.3.58	I-2.3.80		522 (M + H − BOC)+	0.87	Z018_S04

TABLE 24.1-continued

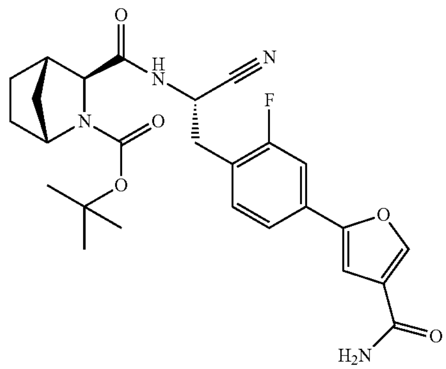
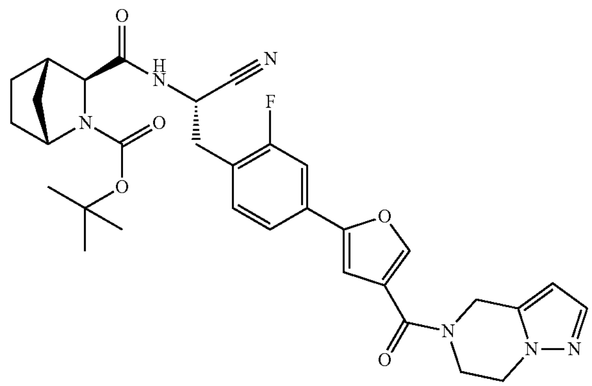
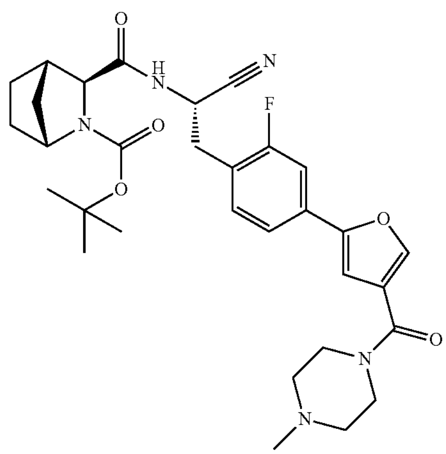
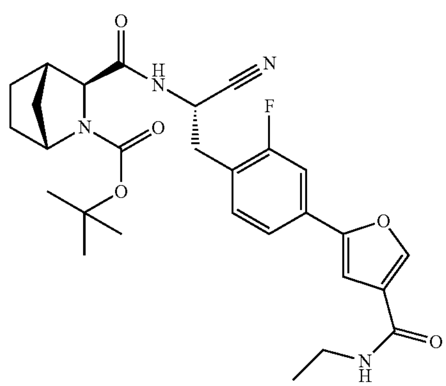
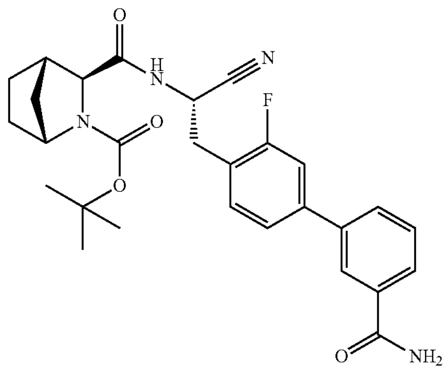
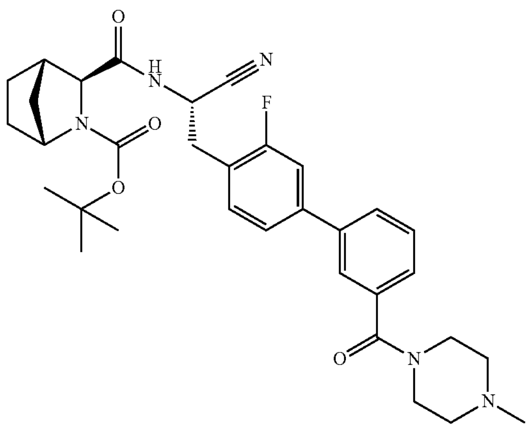
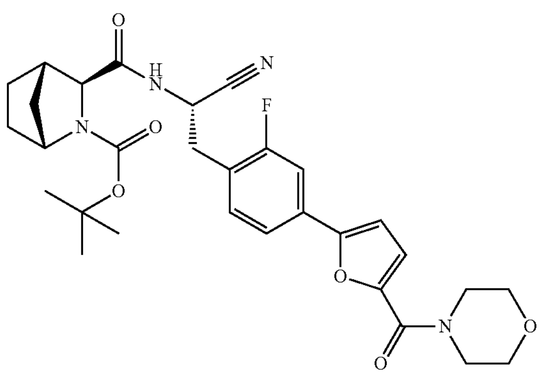
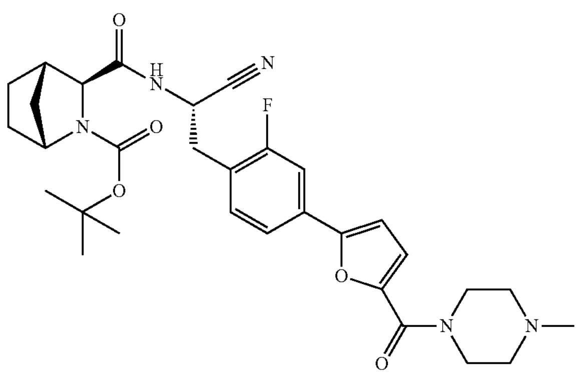
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.59	I-2.3.81		397 (M + H − BOC)+	0.86	Z018_S04
I-4.3.60	I-2.3.81		503 (M + H − BOC)+	0.88	Z011_S03
I-4.3.61	I-2.3.81		480 (M + H − BOC)+	0.74	Z018_S04
I-4.3.62	I-2.3.81		425 (M + H − BOC)+	0.91	Z018_S04

TABLE 24.1-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-4.3.63	I-2.3.82		407 (M + H − BOC)+	1.02	Z018_S04
I-4.3.64	I-2.3.82		490 (M + H − BOC)+	0.76	Z018_S04
I-4.3.65	I-2.3.80		467 (M + H − BOC)+	0.91	Z018_S04
I-4.3.66	I-2.3.80		480 (M + H − BOC)+	0.73	Z018_S04

The reaction conditions for I-4.3.63 differ: I-2.3.82 (100 mg, 0.197 mmol), HATU (82.4 mg, 0.217 mmol) and DIPEA (68 μL, 2 eq) are dissolved in DMF. The mixture is stirred at r.t. for 30 min. Ammonium chloride (63.2 mg, 1.182 mmol) and DIPEA (204 μL, 6 eq) are added, and the reaction mixture is stirred at r.t. for 3 h. The product mixture is separated by HPLC-MS (Waters, 30×100 mm, 10 μM, xBridge RP18, ACN/water/TFA). The fractions are combined and freeze-dried. Yield: 27%.

The reaction conditions for I-4.3.65 and I-4.3.66 differ: DCM is used as solvent instead of DMF.

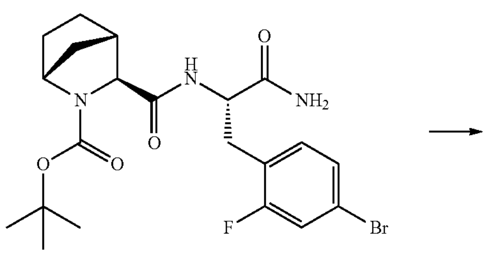
Step 4: Synthesis of Example 4

I-4.3 (348 mg, 0.64 mmol) in formic acid is stirred for 10 min at 40° C. The reaction solution is diluted with DMF and directly purified by reversed phase HPLC. Yield 86%, m/z 442 [M+H]+, rt 0.65 min, LC-MS Method Z018_S04.

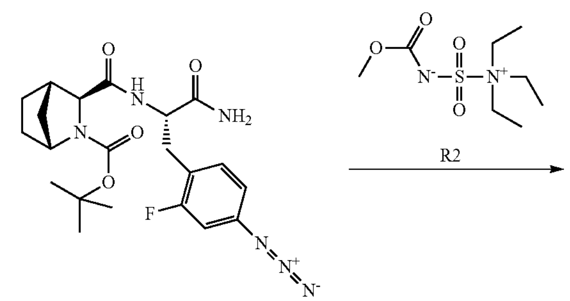
Method A4

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-[4-(1H-indol-5-yl)triazol-1-yl]phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

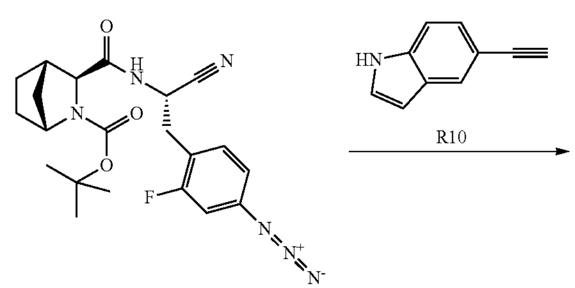
Example 5



I-2.1

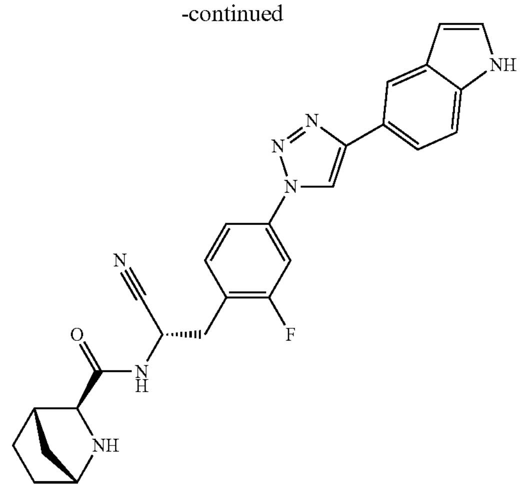


I-5.1



I-5.2

-continued



Example 5

Step 1: Synthesis of Intermediate I-5.1

I-2.1 (2.26 g, 4.7 mmol), sodium azide (0.61 g, 9.3 mmol), trans-(1R,2R)—N,N'-bismethyl-1,2-cyclohexane diamine (147 μl, 0.93 mmol), copper(I)iodide (89 mg, 0.47 mmol) and L-ascorbic acid sodium salt (92 mg, 0.47 mmol) are dissolved in ethanol/water=7/3 (60 mL). The mixture is heated to 100° C. for 1.5 h. Water and DCM are added to the reaction mixture. The organic layer is washed with water and brine, dried over $MgSO_4$ and concentrated. The residue is purified by reversed phase HPLC. Yield 85% m/z 447 [M+H]+, rt 0.91 min, LC-MS Method Z018_S04.

Step 2: Synthesis of Intermediate I-5.2

To I-5.1 (1.76 g, 3.9 mmol) in anhydrous DCM (30 mL) R2 (2.35 g, 9.9 mmol) is added. The reaction mixture is stirred for 11 h. The reaction mixture is extracted with 0.5M HCl and water. The organic layer is extracted with half saturated Na2CO3 solution, water and brine. The residue is purified by reversed phase HPLC. Yield 54% m/z 329 [M+H]+, rt 0.96 min, LC-MS Method Z018_S04.

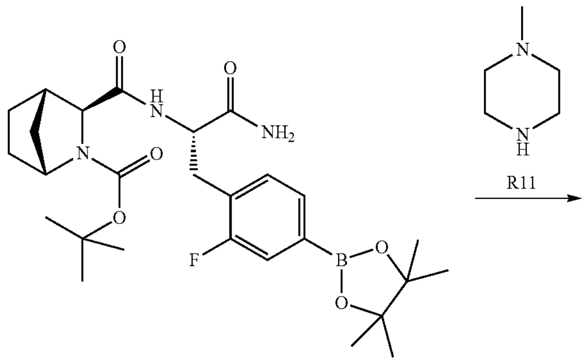
Step 3: Synthesis of Example 5

To R10 (28 mg, 0.20 mmol) in DMSO (1.3 mL) I-5.2 (43 mg, 0.10 mmol) is added. Then copper(II) sulfate pentahydrate (2.2 mg, 0.011 mmol), L-ascorbic acid sodium salt (11 mg, 0.05 mmol) and 100 μL water are added. The reaction mixture is stirred for 12 h. The reaction mixture is diluted with DMF and directly purified by reversed phase HPLC. The achieved substance is dissolved in formic acid, stirred at 40° C. for 10 min and the reaction mixture is purified again by reversed phase HPLC. Yield 34% m/z 470 [M+H]+, rt 0.70 min, LC-MS Method Z018_S04.

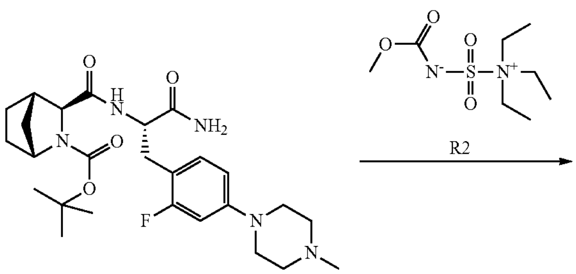
Method A5

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-(4-methylpiperazin-1-yl)phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 6

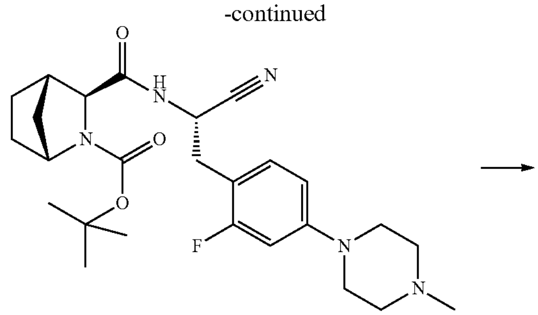


I-3.1

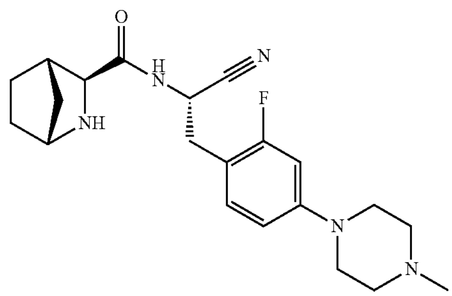


I-6.1

-continued



I-6.2



Example 6

Step 1: Synthesis of Intermediate I-6.1

To I-3.1 (90 mg, 0.20 mmol) in DCM (4 mL), triethylamine (60 μL, 0.43 mmol), R11 (23 μL, 0.21 mmol) and copper(II) acetate (55 mg, 0.30 mmol) are added. The mixture is stirred for 12 h. 7M ammonium solution in methanol is added, the mixture is concentrated. The residue dissolved in acetonitrile and filtrated. The product is purified by reversed phase HPLC. Yield 32%, m/z 504 [M+H]+, rt 1.00 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 24.2 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 24.2

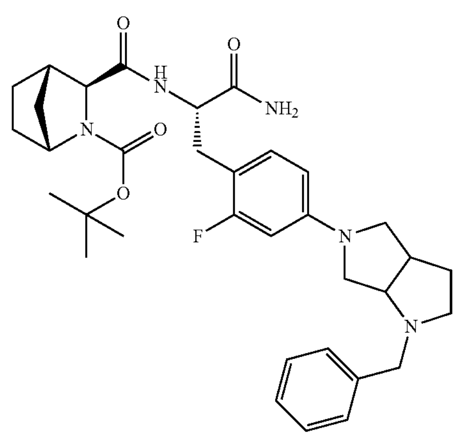
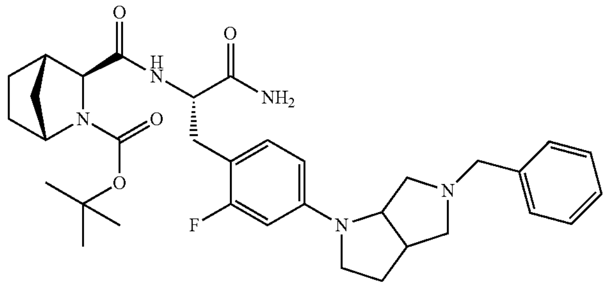
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.89	I-3.1.5		606	1.40	V011_S01

TABLE 24.2-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-3.2.113	I-3.1.5		606	1.37	V011_S01

Step 2: Synthesis of Intermediate I-6.2

To I-6.1 (40 mg, 0.08 mmol) in DCM (1 mL) R2 (35 mg, 0.15 mmol) is added. The reaction mixture is stirred for 12 h. The reaction mixture is concentrated and the residue is purified by reversed phase HPLC. Yield 67%, m/z 486 [M+H]+, rt 1.12 min, LC-MS Method V011_S01.

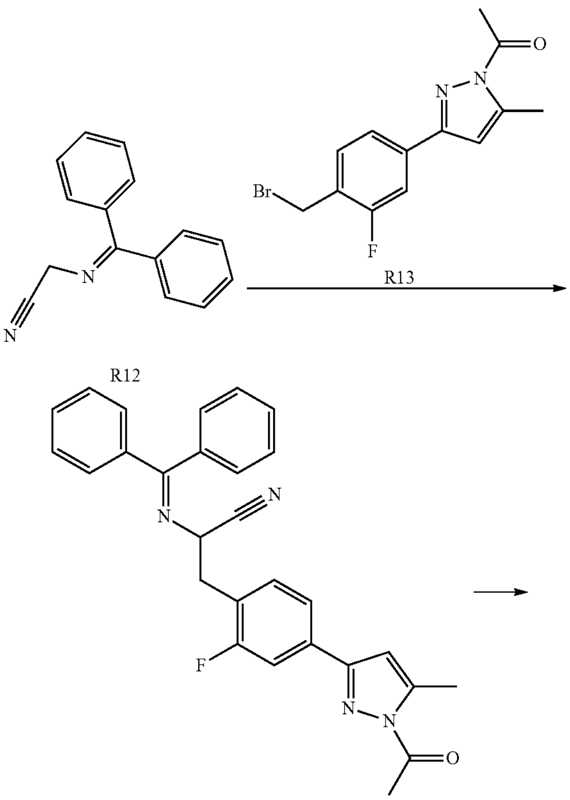
Step 3: Synthesis of Example 6

To I-6.2 (25 mg, 0.05 mmol) in acetonitrile, p-toluenesulfonic acid monohydrate (35 mg, 0.18 mmol) is added and stirred for 12 h. The product is purified by reversed phase HPLC. Yield 86%, m/z 386 [M+H]+, rt 0.98 min, LC-MS Method V011_S01.

Method B

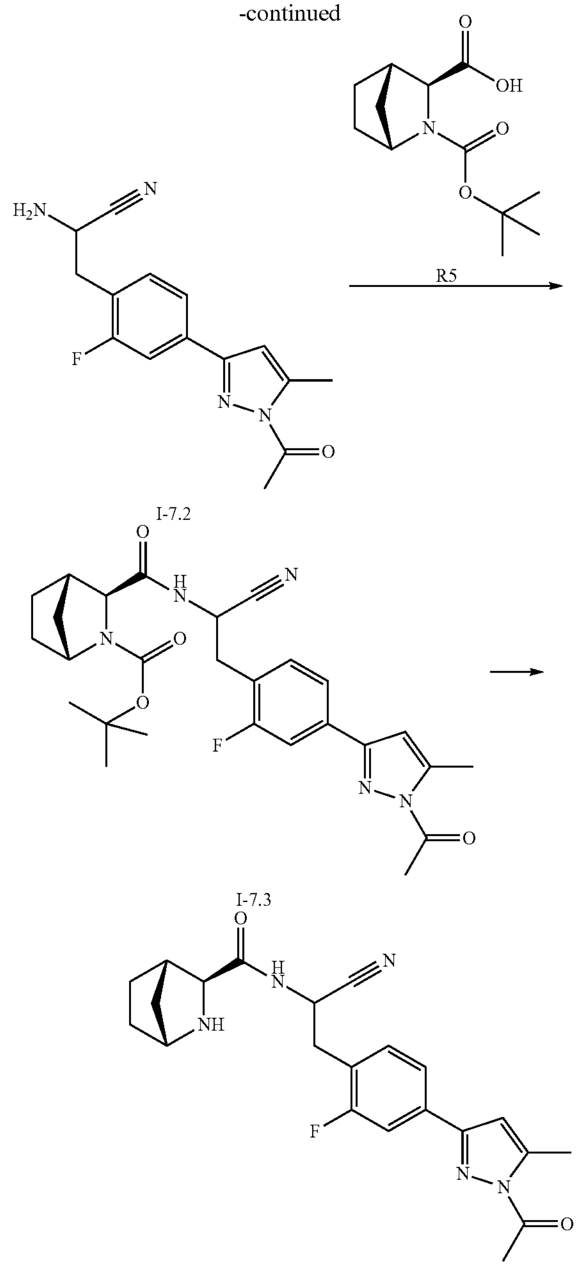
Synthesis of (1S,2S,4R)—N-[2-[4-(1-acetyl-5-methyl-pyrazol-3-yl)-2-fluoro-phenyl]-1-cyano-ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 7



R12 R13 I-7.1

-continued



R5 I-7.2 I-7.3 Example 7

Step 1: Synthesis of Intermediate I-7.1

R12 (340 mg, 1.54 mmol), R13 (480 mg, 1.54 mmol), benzyltrimethylammonium chloride (29 mg, 0.15 mmol) and DCM (10 mL) are put together. Under stirring water (250 μL) and sodium hydroxide solution (19 mol/L, 146 μL) are added. The reaction mixture is stirred for 1 h. Half saturated brine and DCM are added. The organic layer is concentrated and purified by reversed phase HPLC. Yield 22%. m/z 451 [M+H]+, rt 1.48 min, LC-MS Method V011_S01.

The following intermediate as shown in Table 25 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 25

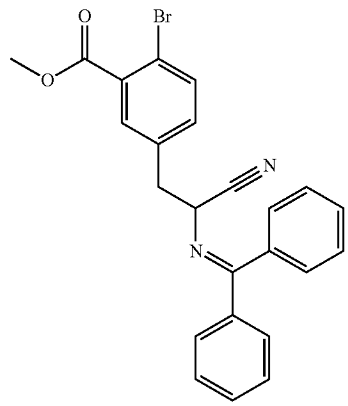
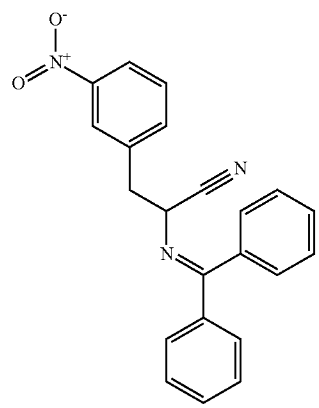
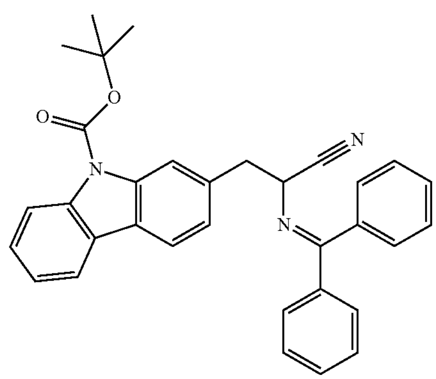
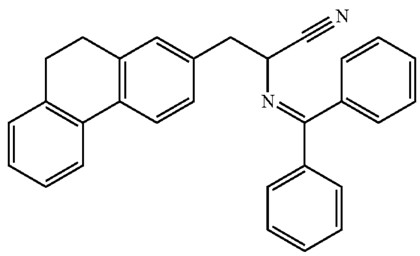
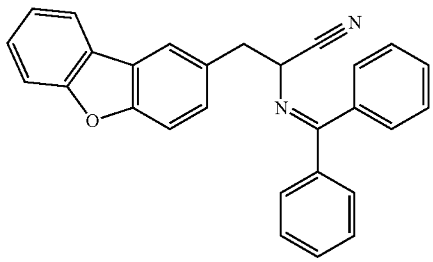
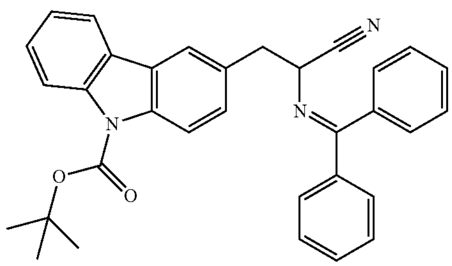
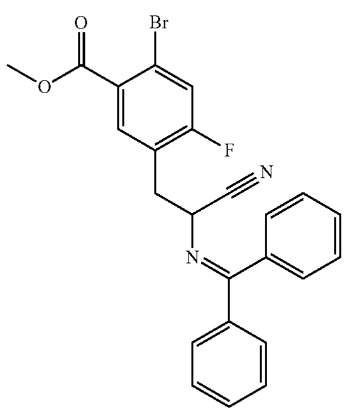
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-7.1.1		447/449	0.78	X012_S01
I-7.1.2		356	0.75	X012_S01
I-7.1.3		500	0.95	X012_S01

TABLE 25-continued

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-7.1.4		413	0.90	X012_S01
I-7.1.5		401	0.86	X012_S01
I-7.1.6		500	0.95	X012_S01
I-7.1.7		466	0.82	X011_S01

Step 2: Synthesis of Intermediate I-7.2

To I-7.1 (155 mg, 0.34 mmol) in dioxane (6 mL) aq. HCl (1 mol/L, 361 μL) is added. The reaction mixture is stirred for 1 h. 135 μL aq. HCl (1 M) is added and stirred for additional 30 min. The product is purified by reversed phase HPLC. Yield >95%. m/z 287 [M+H]+, rt 1.01 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 26 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 26

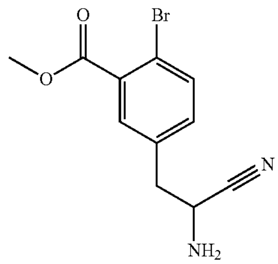
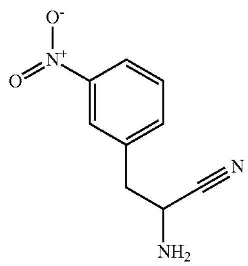
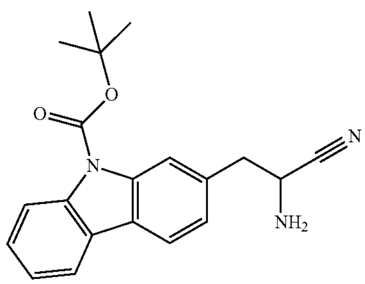
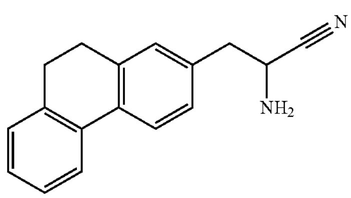
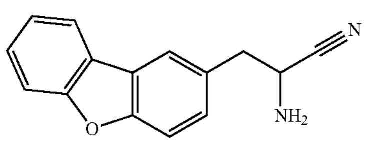
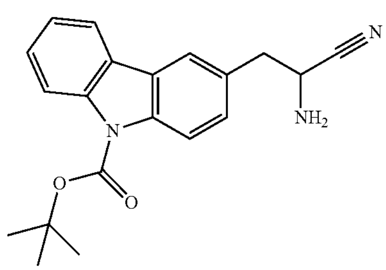
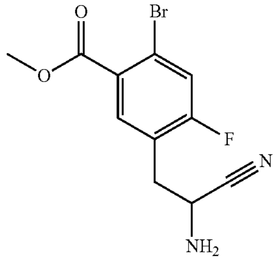
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-7.2.1	I-7.1.1		284/286	0.48	X012_S01
I-7.2.2	I-7.1.2		n.d.	n.d.	n.d.
I-7.2.3	I-7.1.3		336	0.56	X012_S01
I-7.2.4	I-7.1.4		249	0.47	X012_S01
I-7.2.5	I-7.1.5		227	0.43	X012_S01
I-7.2.6	I-7.1.6		336	0.55	X012_S01

TABLE 26-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-7.2.7	I-7.1.7		318/320 (M + H2O)	0.48	X011_S02

Step 3: Synthesis of Intermediate I-7.3

To R5 (50 mg, 0.21 mmol) in DMF (1.5 mL) HATU (87 mg, 0.23 mmol) and diisopropylethylamine (143 μL, 0.83 mmol) are added and the reaction mixture is stirred for 15 min. Then intermediate I-7.2 (87 mg, 0.22 mmol) is added and the mixture stirred for 12 h. The reaction solution is purified by reversed phase HPLC. Yield 81%, m/z 510/454/410 [M+H]+, rt 1.28 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 27 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 27

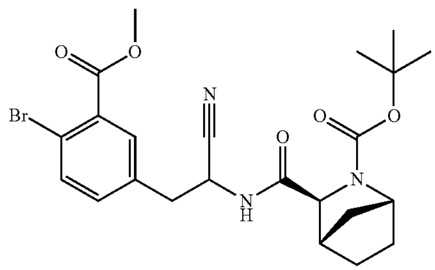
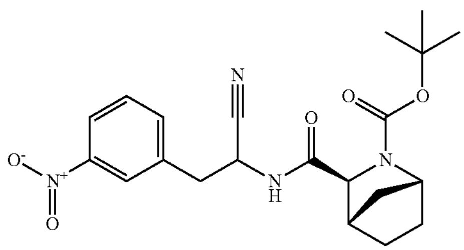
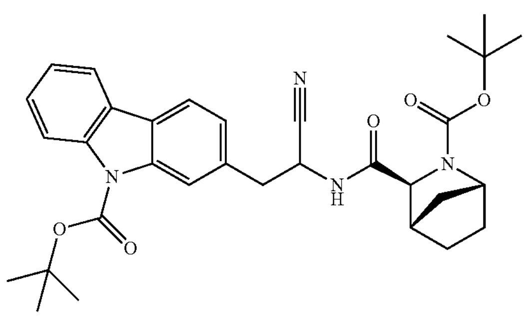
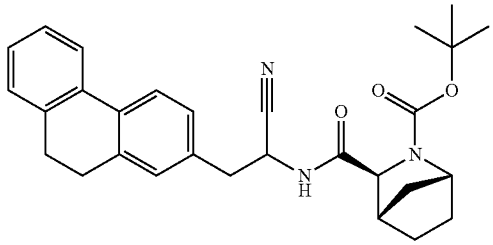
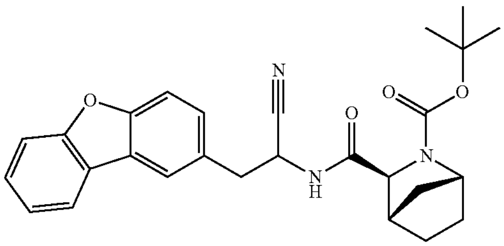
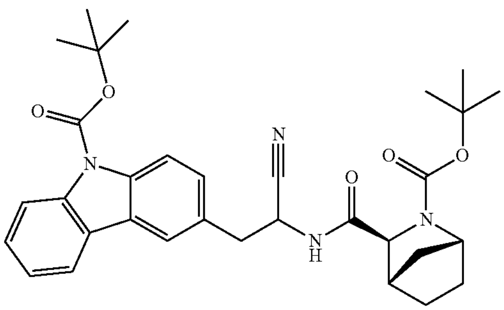
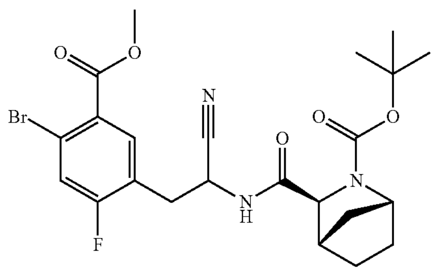
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-7.3.1	I-7.2.1		506/508	0.66	X012_S01
I-7.3.2	I-7.2.2		415	0.61	X012_S01
I-7.3.3	I-7.2.3		559	0.84	X012_S01

TABLE 27-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-7.3.4	I-7.2.4		472	0.78	X012_S01
I-7.3.5	I-7.2.5		460	0.74	X012_S01
I-7.3.6	I-7.2.6		559	0.84	X012_S01
I-7.3.7	I-7.2.7		524/526	0.71	X011_S02

Intermediate I-7.3.7 is separated according to method "Chiral SFC F" to give the following compounds of Table 28

TABLE 28

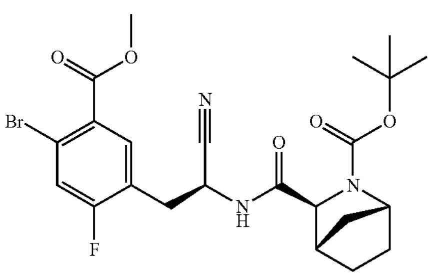
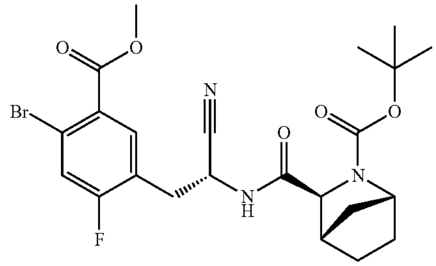
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	SFC method
I-7.3.8	I-7.3.7		n.d.	2.432	I_IC_20_MEOH_NH3.M

TABLE 28-continued

Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	SFC method
I-7.3.9	I-7.3.7		n.d.	1.946	I_IC_20_MEOH_NH3.M

Step 4: Synthesis of Example 7

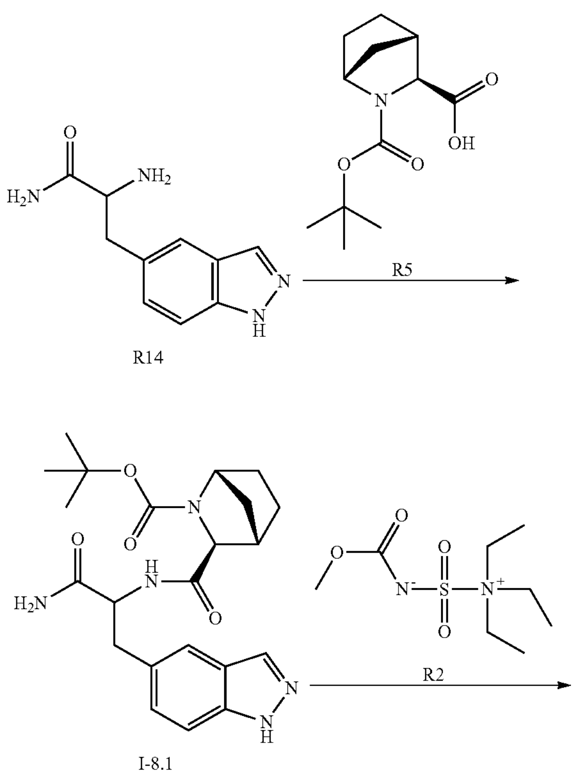
To I-7.3 (40 mg, 0.08 mmol) in acetonitrile (1 mL) sodium iodide (14 mg, 0.09 mmol) and chlorotrimethylsilane (12 μL, 0.09 mmol) are added. The mixture is stirred for 20 min. The product is purified by reversed phase HPLC. Yield 39%, m/z 410 [M+H]+, rt 0.96 min, LC-MS Method V018_S01

For example 58 I-7.3 is stirred in formic acid at 50° C. for 10 min in a pressure vessel.

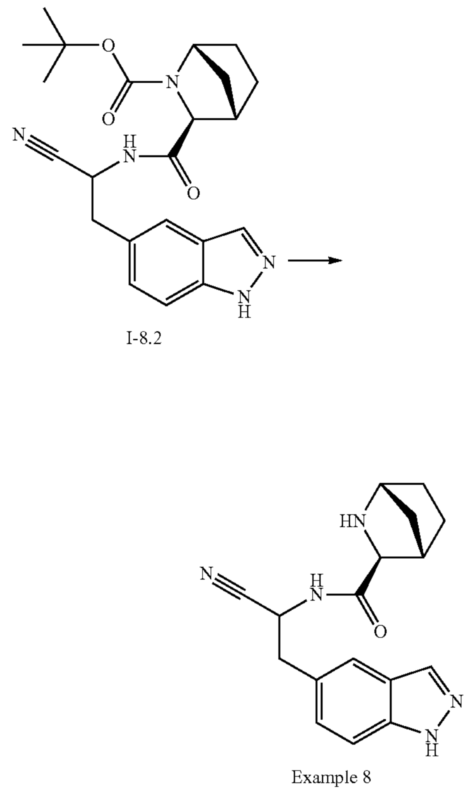
Method C

Synthesis of (1S,2S,4R)—N-[1-cyano-2-(1H-indazol-5-yl)ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 8



-continued

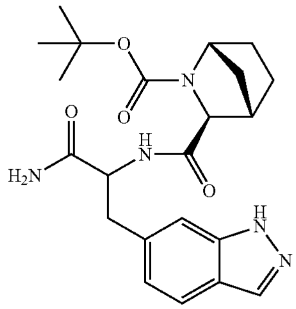
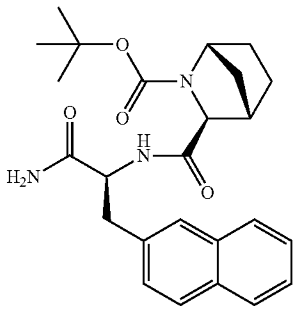
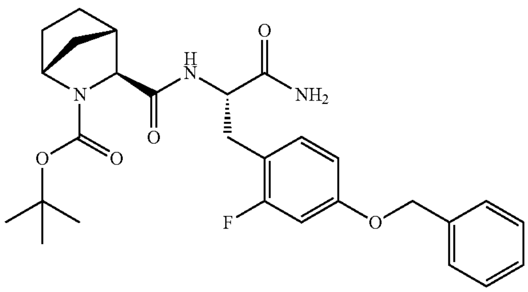
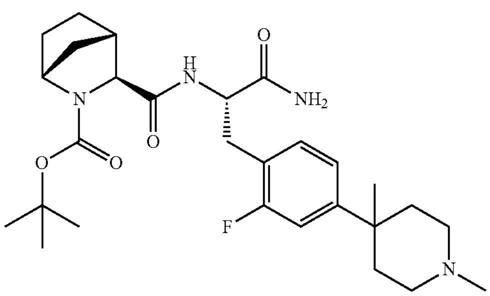


Step 1: Synthesis of Intermediate I-8.1

To R5 (102 mg, 0.42 mmol) in DMF (3 mL) diisopropylethylamine (296 μL, 1.70 mmol) and TBTU (136 mg, 0.23 mmol) are added and the reaction mixture is stirred for 15 min. Then R14 (135 mg, 0.42 mmol) is added and the mixture is stirred for additional 1 h. Water is added to the reaction mixture and extracted with ethyl acetate. The organic layer is washed with brine, dried over Na2SO4 and concentrated. Yield 70%.

The following intermediate as shown in Table 29 is synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the amide group):

TABLE 29

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-8.1.1	R14.1		428	0.91	V011_S01
I-8.1.2	R14.2		437	0.64	X012_S01
I-8.1.3	R47		512	1.26	V011_S01
I-8.1.4	R49		517	1.09	V011_S01

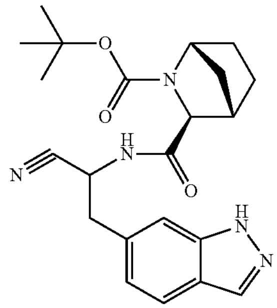
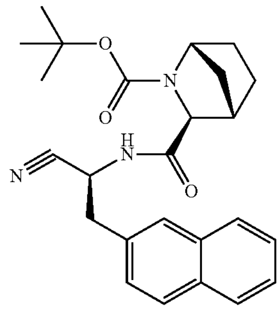
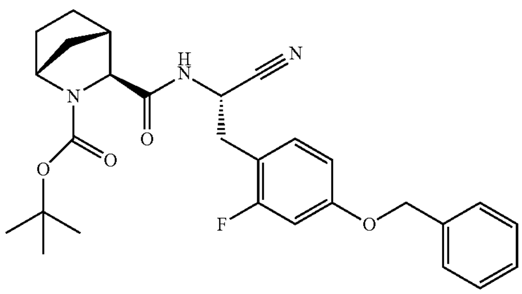
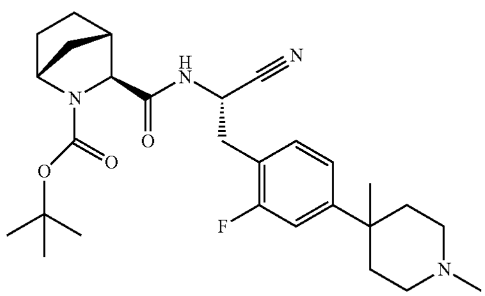
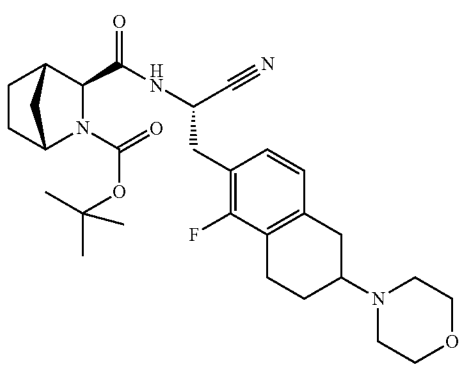
The reaction conditions for I-8.1.3 and I-8.1.4 differ: HATU is used instead of TBTU.

Step 2: Synthesis of Intermediate I-8.2

To I-8.1 (126 mg, 0.29 mmol) in DCM (1 mL) R2 (155 mg, 0.65 mmol) is added. The reaction mixture is stirred for 12 h and then concentrated. Yield 100% m/z 310/354/410 [M+H]+, rt 1.02 min, LC-MS Method V012_S01.

The following intermediates as shown in Table 30 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 30

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-8.2.1	I-8.1.1		n.d	n.d	n.d
I-8.2.2	I-8.1.2		420	0.70	X012_S01
I-8.2.3	I-8.1.3		494	1.37	V011_S01
I-8.2.4	I-8.1.4		499	1.22	V011_S01
I-8.2.5	I-24.3.2		527	0.66	X011_S03

Step 3: Synthesis of Example 8

To I-8.1 (120 mg, 0.29 mmol) in acetonitrile (7 mL) sodium iodide (132 mg, 0.88 mmol) and chlorotrimethylsilane (106 μl, 0.88 mmol) are added. The mixture is stirred for 12 h, then methanol (7 mL) is added, stirred for 1 h and then concentrated. The residue is dissolved in ethyl acetate, washed with water and brine, dried over Na_2SO_4 and concentrated. The product is purified by reversed phase HPLC. Yield 19%, m/z 310 [M+H]+, rt 0.86 min, LC-MS Method V011_S01.

Method D

Synthesis of (1S,2S,4R)—N-[1-cyano-2-(6-oxo-5H-phenanthridin-8-yl)ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

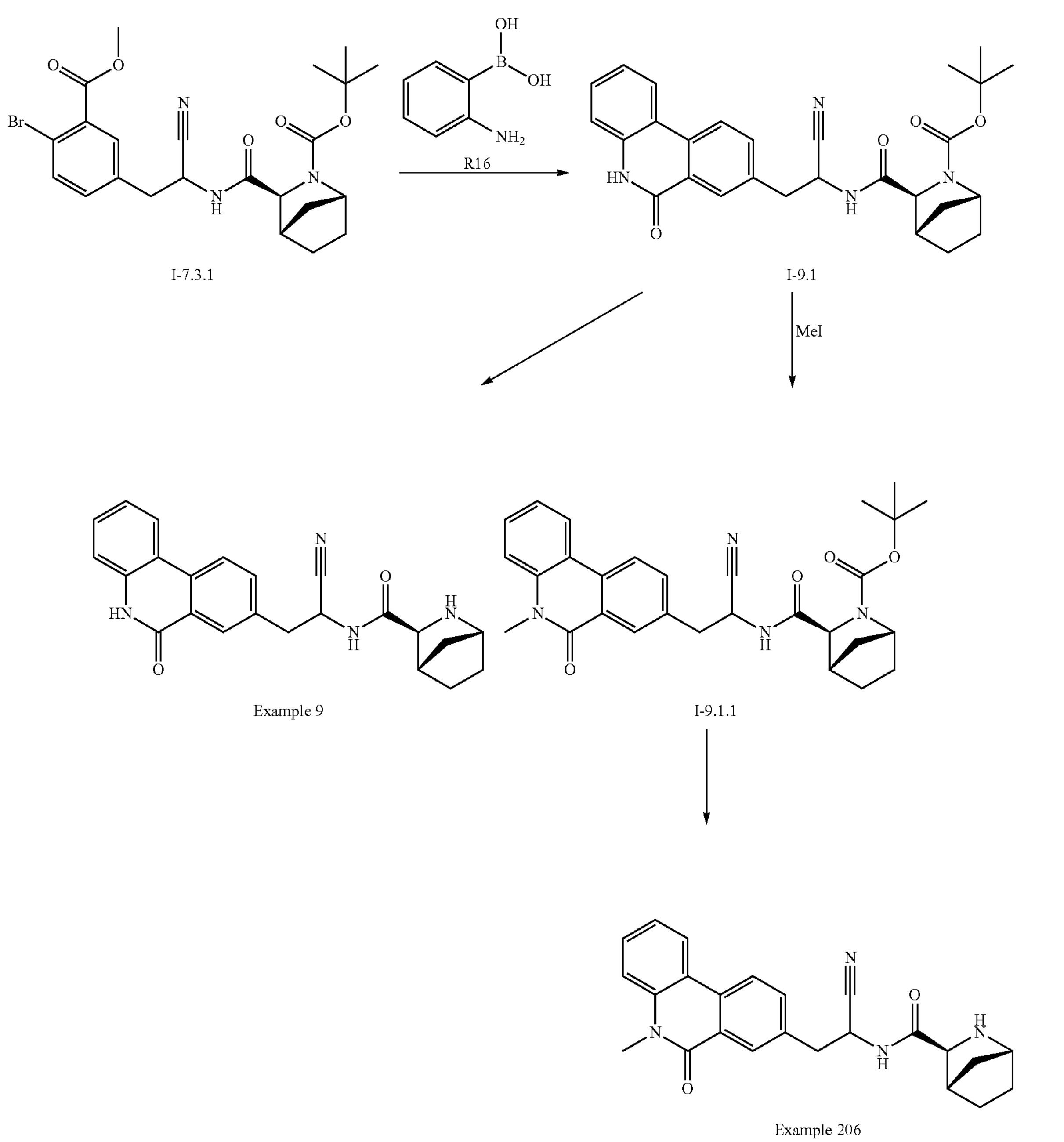
Example 9

Step 1: Synthesis of Intermediate I-9.1

I-7.3.1 (200 mg, 0.39 mmol) and R16 (65 mg, 0.47 mmol) in acetonitrile (5 mL) is purged with argon. 1,1-Bis(di-tert-butylphosphino)ferrocene palladium dichloride (26 mg, 0.04 mmol) and aq. sodium carbonate solution (2 mol/L, 395 μL) are added and heated to 70° C. for 3 h. DCM and water are added to the reaction mixture. The organic layer is dried over $MgSO_4$ and concentrated. The product is purified by reversed phase HPLC. Yield 50% m/z 487 [M+H]+, rt 0.60 min, LC-MS Method X012_S01.

Step 2: Synthesis of Example 9

To I-9.4 (115 mg, 0.24 mmol) in acetonitrile (5 mL) sodium iodide (106 mg, 0.71 mmol) and chlorotrimethylsilane (90 μL, 0.71 mmol) are added. The mixture is stirred for 90 min.



The product is purified by reversed phase HPLC. Yield 32%, m/z 387 [M+H]+, rt 0.39 min, LC-MS Method X012_S01.

Synthesis of Intermediate I-9.1.1

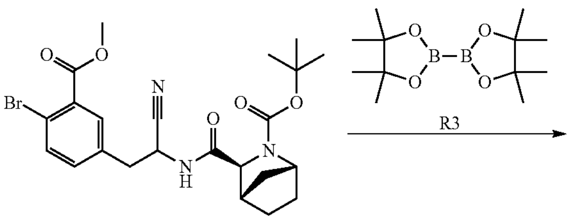
I-9.1 (100 mg, 0.2 mmol) and MeI (14.2 μL, 0.23 mmol) are dissolved in 2 mL DMF, and NaH (9.04 mg, 0.23 mmol, as 60% suspension in paraffin oil) is added. After stirring for 12 h at r.t., the mixture is diluted with methanol, filtered and purified by HPLC. The product fractions are freeze-dried to yield 42 mg (41%) I-9.1.1. m/z 501 [M+H]+, rt 0.65 min, LC-MS Method X012_S01.

Boc deprotection to Example 206 is performed in analogy to the synthesis of Example 9.

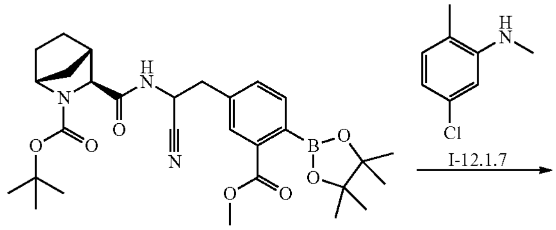
Method D1

Synthesis of (1S,2S,4R)—N-[2-(3-chloro-5-methyl-6-oxo-phenanthridin-8-yl)-1-cyano-ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 305

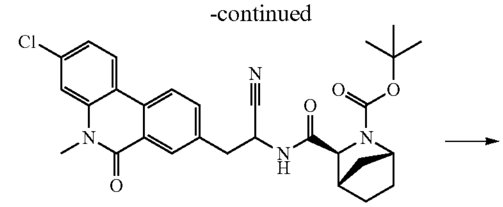


I-7.3.1

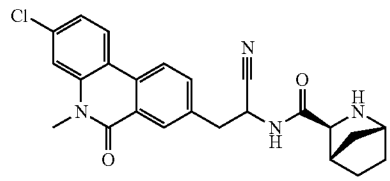


I-18.1(R,S)

-continued



I-18.2(R,S)



Example 305

Step 1: Synthesis of Intermediate I-18.1

To I-7.3.1 (4.0 g, 7.9 mmol) in anhydrous dioxane (50 mL) R3 (2.93 g, 11.5 mmol) and potassium acetate (2.27 g, 23.2 mmol) are added. The mixture is purged with argon, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichlormethan complex ($PdCl_2$(dppf)) (0.66 g, 0.81 mmol) is added to the mixture and heated to 70° C. overnight. The reaction mixture is diluted with DCM and water. The organic layer is separated, dried and concentrated. The residue is purified by reversed phase HPLC. Yield 71% m/z 554 [M+H]+, rt 0.74 min, LC-MS Method X011_S03.

The following intermediates as shown in Table 31 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 31

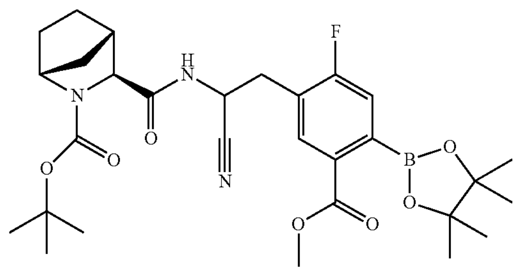
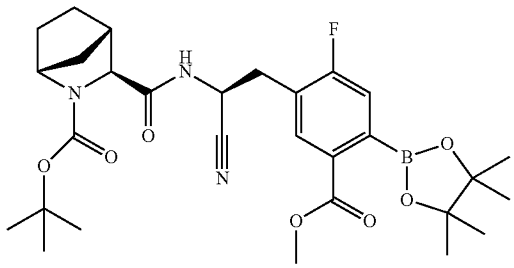
Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.1.1	I-7.3.7		572	0.72	X011_S02

TABLE 31-continued

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.1.2	I-7.3.8		572	0.74	X012_S01

Step 2: Synthesis of Intermediate I-18.2

To I-18.1 (150 mg, 0.27 mmol) in anhydrous ACN (5 mL) (5-chloro-2-iodophenyl)methanamine (72.498 mg, 0.27 mmol) is added and purged with argon. 1,1bis(di-tert.butylphosphino)ferrocene palladium dichloride (17.66 mg, 0.027 mmol) and a solution of sodium carbonate in water 2 mol/L (0.271 mL, 0.54 mmol) are added, purged again with argon and heated to 70° C. for 6 h. The reaction mixture is diluted with DCM and water. The organic layer is separated, dried and concentrated. The crude residue is used for the next step without further purification. Yield 93% m/z 536[M+H]+, rt 0.71 min, LC-MS Method X012_S01.

The following intermediates as shown in Table 32 are synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 32

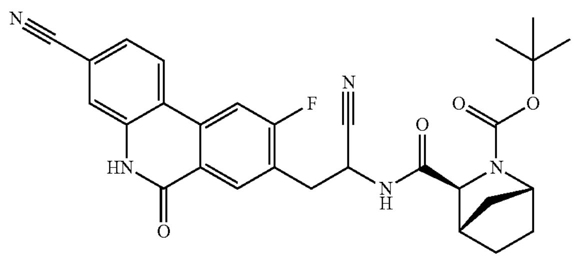
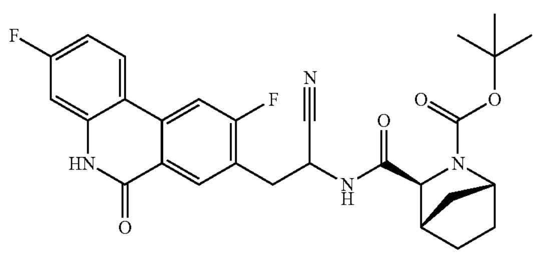
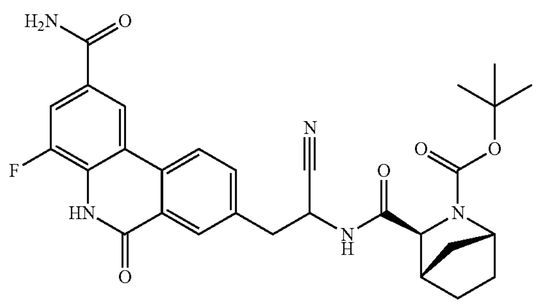
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.1	I-18.1.1		530	0.62	X011_S03
I-18.2.2	I-18.1.1		523	0.66	X011_S02
I-18.2.3	I-18.1		548	0.48	X011_S03

TABLE 32-continued

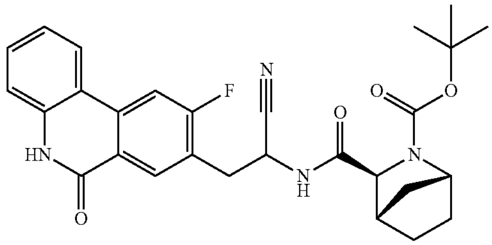
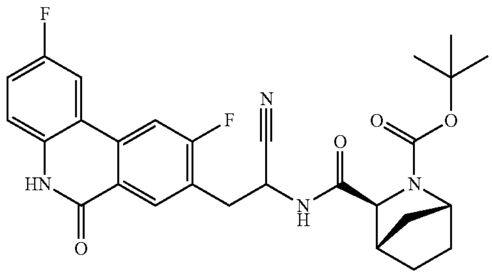
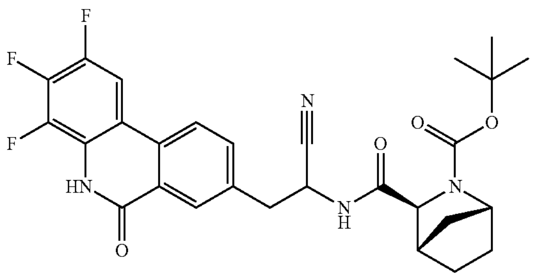
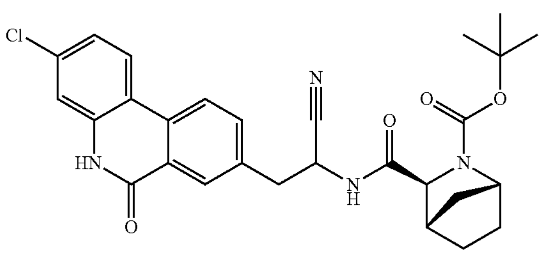
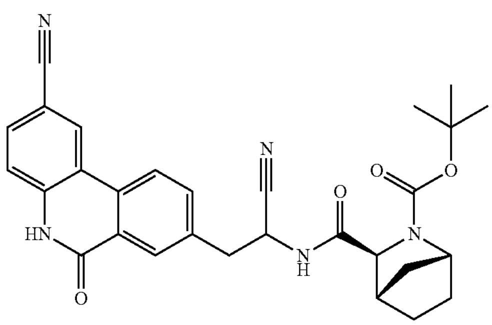
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.4	I-18.1.1		505	0.65	X011_S02
I-18.2.5	I-18.1.1		523	0.66	X011_S02
I-18.2.6	I-18.1		541	0.69	X012_S02
I-18.2.7	I-18.1		522	0.65	X012_S01
I-18.2.8	I-18.1		512	0.57	X012_S01

TABLE 32-continued

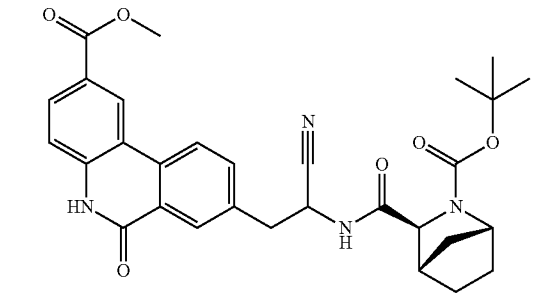
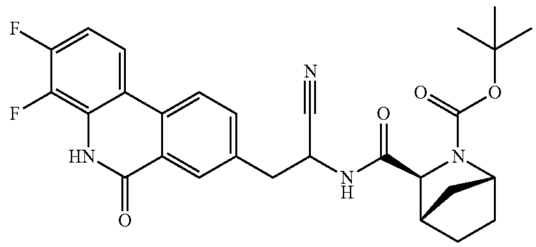
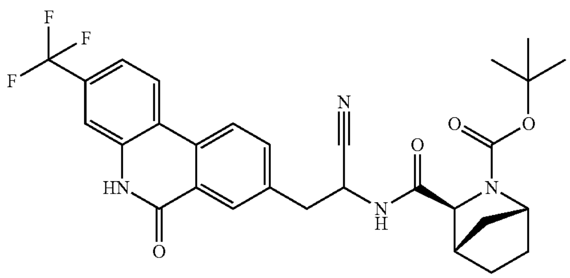
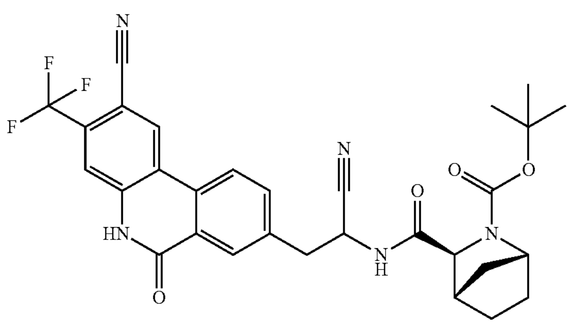
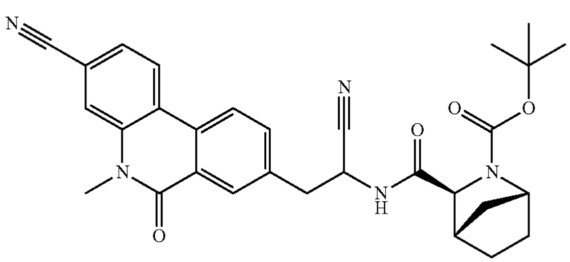
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.9	I-18.1		545	0.61	X011_S03
I-18.2.10	I-18.1		523	0.68	X012_S02
I-18.2.11	I-18.1		555	0.69	X011_S03
I-18.2.12	I-18.1		580	0.60	X011_S03
I-18.2.13	I-18.1		526	0.64	X012_S01

TABLE 32-continued

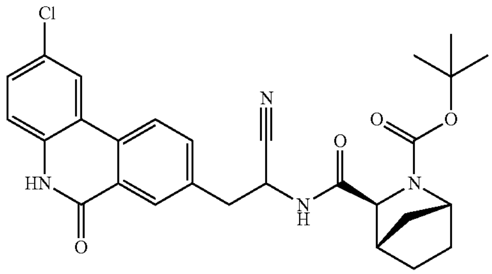
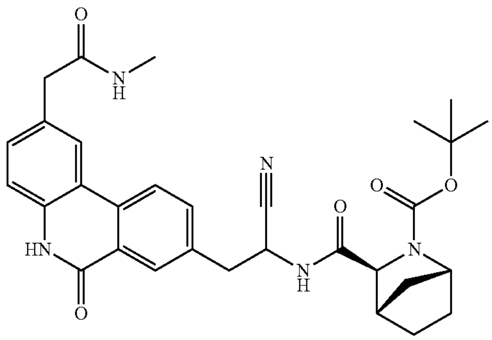
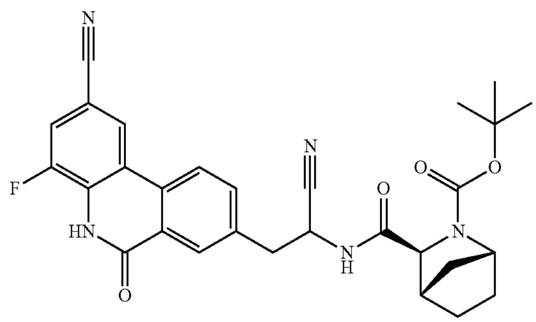
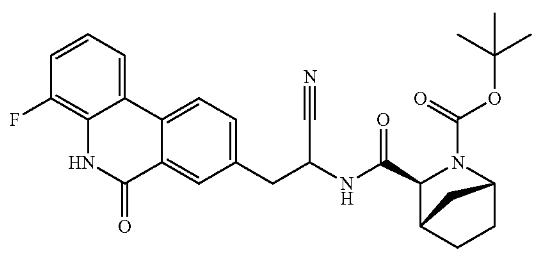
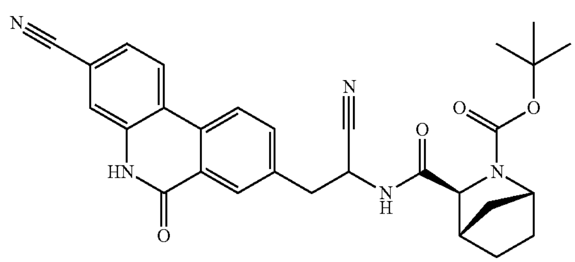
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.14	I-18.1		521	0.67	X011_S03
I-18.2.15	I-18.1		558	0.50	X012_S01
I-18.2.16	I-18.1		530	0.54	X011_S03
I-18.2.17	I-18.1		505	0.61	X012_S01
I-18.2.18	I-18.1		512	0.45	X012_S01

TABLE 32-continued

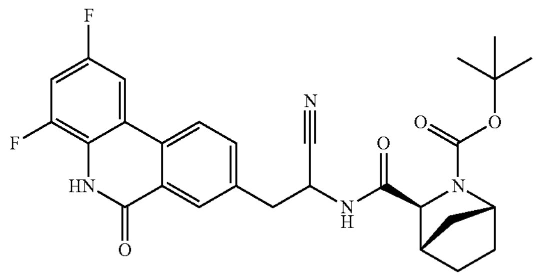
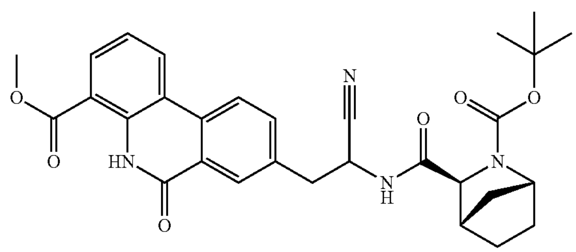
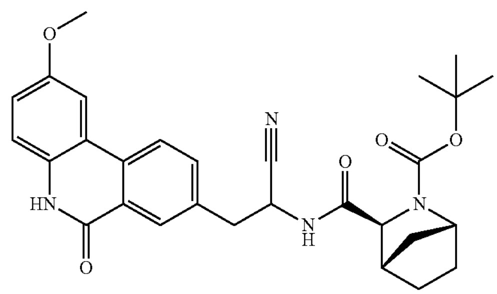
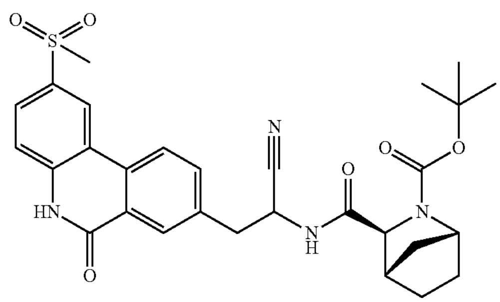
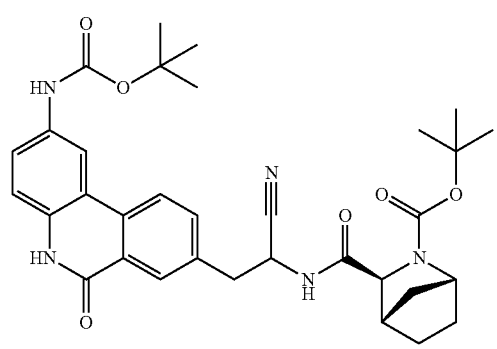
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.19	I-18.1		523	0.62	X012_S01
I-18.2.20	I-18.1		545	0.61	X011_S03
I-18.2.21	I-18.1		517	0.61	X011_S03
I-18.2.22	I-18.1		565	0.53	X012_S01
I-18.2.23	I-18.1		602	0.66	X012_S01

TABLE 32-continued

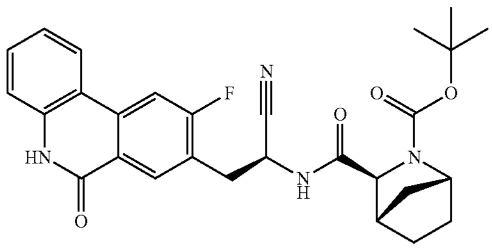
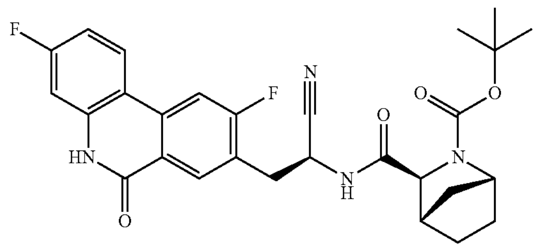
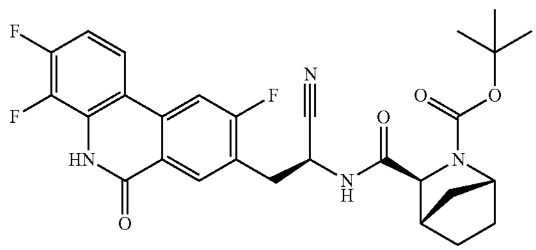
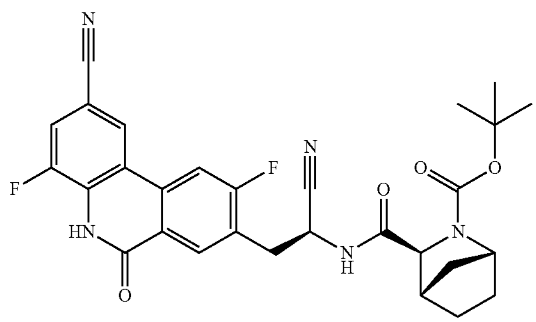
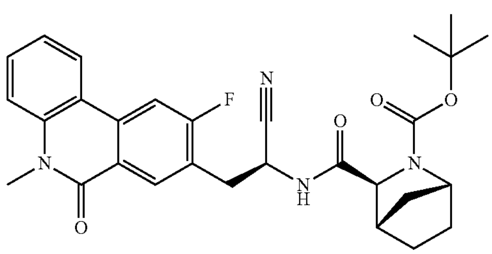
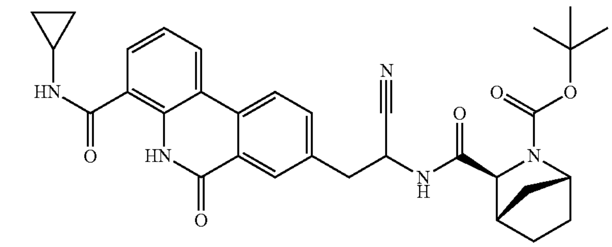
Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.24	I-18.1.2		505	0.61	X012_S01
I-18.2.25	I-18.1.2		523	0.63	X012_S01
I-18.2.26	I-18.1.2		541	0.64	X012_S01
I-18.2.27	I-18.1.2		548	0.60	X012_S01
I-18.2.28	I-18.1.2		519	0.67	X012_S01

TABLE 32-continued

Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-18.2.29	I-18.1		570	0.59	X012_S01

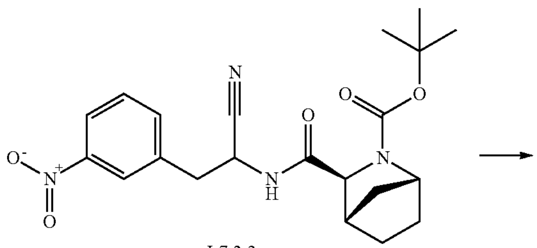
Step 3: Synthesis of Example 305

To I-18.2 (270 mg, 0.25 mmol) in THF (3 mL) methanesulfonic acid (81.87 μL, 1.26 mmol) is added and the reaction mixture is stirred at r.t. overnight. The reaction mixture is concentrated and the residue is purified by reversed phase HPLC. Yield 14% m/z 435 [M+H]+, rt 0.48 min, LC-MS Method X012_S01.

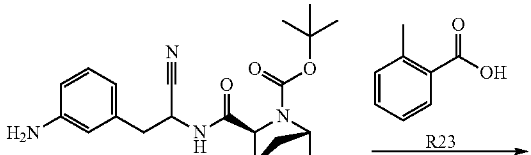
Method E

Synthesis of (1S,2S,4R)—N-[1-cyano-2-(6-oxo-5H-phenanthridin-3-yl)ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide and (1S,2S,4R)—N-[1-cyano-2-(6-oxo-5H-phenanthridin-1-yl)ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

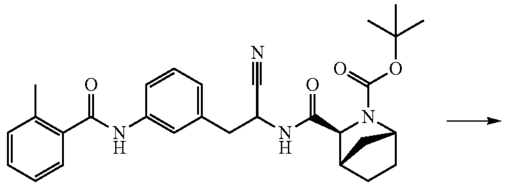
Example 123 and 128



I-7.3.2

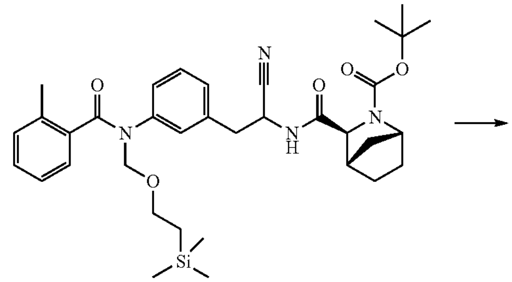


I-10.1

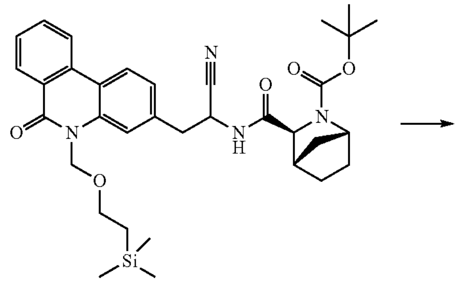


I-10.2

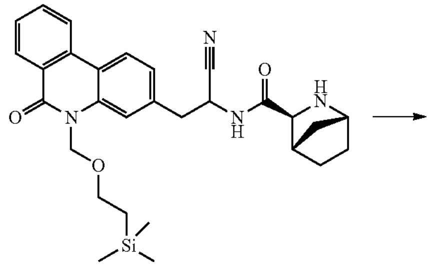
-continued



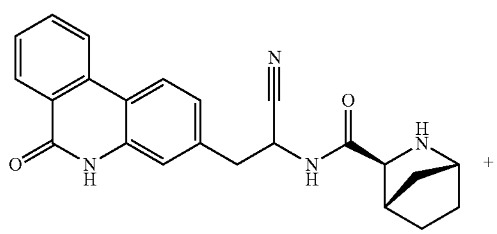
I-10.3



I-10.4

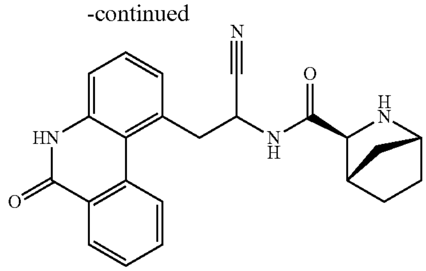


I-10.5



Example 123

-continued



Example 128

Step 1: Synthesis of Intermediate I-10.1

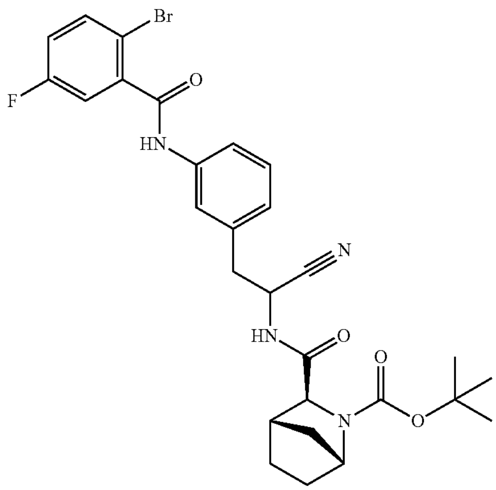
To I-7.3.2 (6.0 g, 14.5 mmol) in ethyl acetate (100 mL) tin(II)chloride dihydrate (16.3 g, 72.4 mmol) is added. The reaction mixture is stirred for 12 h. The mixture is set basic with potassium carbonate and aq. sodium hydroxide solution. The organic layer is separated, is dried over $MgSO_4$ and is concentrated. The residue is purified by reversed phase HPLC. Yield 32% m/z 385 [M+H]+, rt 0.42 min, LC-MS Method X012_S01.

Step 2: Synthesis of Intermediate I-10.2

To R23 (0.70 g, 2.81 mmol) in DCM (20 mL) diisopropylethylamine (1.20 mL, 7.02 mmol) and HATU (1.09 g, 2.81 mmol) are added and the reaction mixture is stirred for 7 min. Then intermediate I-10.1 (0.90 g, 2.34 mmol) is added and the mixture is stirred for additional 12 h. The mixture is concentrated and the residue is purified by flash chromatography (cyclohexane/ethyl acetate=70/30). Yield 90% m/z 615 [M+H]+, rt 0.66 min, LC-MS Method X012_S01.

The following intermediate as shown in Table 33 is synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 33

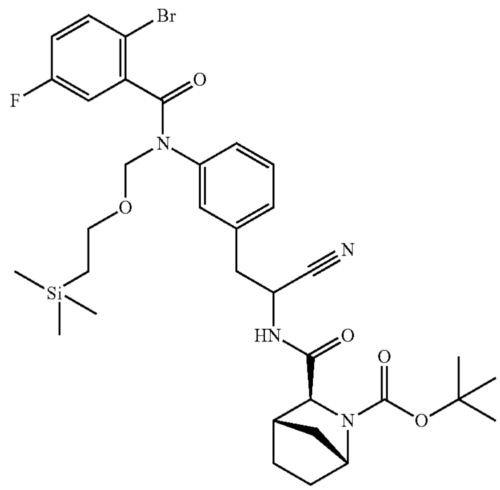
Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-10.2.1	I-10.1		585/587	0.67	X012_S01

Step 3: Synthesis of Intermediate I-10.3

To I-10.2 (800 mg, 1.30 mmol) in DMF (20 mL) sodium hydride (58 mg, 1.43 mmol) is added and the reaction mixture is stirred for 10 min. Then 2-(trimethylsilyl)ethoxymethylchloride (0.25 mL, 1.43 mmol) is added and the mixture is stirred for additional 2 h. Water and DCM is added to the mixture and the organic layer is concentrated. The residue is purified by reversed phase HPLC. Yield 26% m/z 745 [M+H]+, rt 0.85 min, LC-MS Method X012_S01.

The following intermediate as shown in Table 34 is synthesized in a similar fashion from the appropriate intermediate:

TABLE 34

Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-10.3.1	I-10.2.1		715/717	0.84	X012_S01

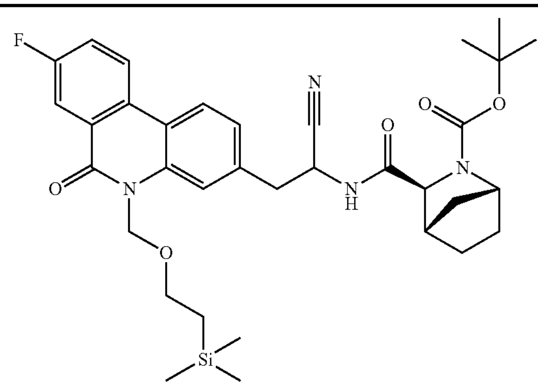
Step 4: Synthesis of Intermediate I-10.4

To I-10.3 (200 mg, 0.27 mmol) in anhydrous DMF (10 mL) tetrakis(triphenylphosphine)palladium (16 mg, 0.01 mmol) and sodium carbonat (58 mg, 0.55 mmol) is added. The reaction mixture is heated to 150° C. for 5 h. Water and ethyl acetate is added to the mixture. The organic layer is dried over $MgSO_4$ and is concentrated. The residue is purified by reversed phase HPLC. Yield 34% m/z 617 [M+H]+, rt 0.84 min, LC-MS Method X012_S01.

During this ring cyclization both isomeres are obtained; but it is first possible to separated them by reversed phase HPLC on the last step (see step 6).

The following intermediate as shown in Table 35 is synthesized in a similar fashion from the appropriate intermediate:

TABLE 35

Intermediate	Educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-10.4.1	I-10.3.1		635	0.86	X012_S01

Step 5: Synthesis of Intermediate I-10.5

To I-10.4 (57 mg, 0.09 mmol) in acetonitrile (5 mL) sodium iodide (42 mg, 0.28 mmol) and chlorotrimethylsilane (35 μL, 0.28 mmol) are added. The mixture is stirred for 90 min. Then methanol (5 mL) is added and the mixture is stirred for additional 15 min. The mixture is concentrated and DCM and water is added to the residue. The organic layer is separated, is dried over $MgSO_4$ and concentrated again. The crude product is carried on with step 6. Yield >95%, m/z 517 [M+H]+, rt 0.62 min, LC-MS Method X012_S01.

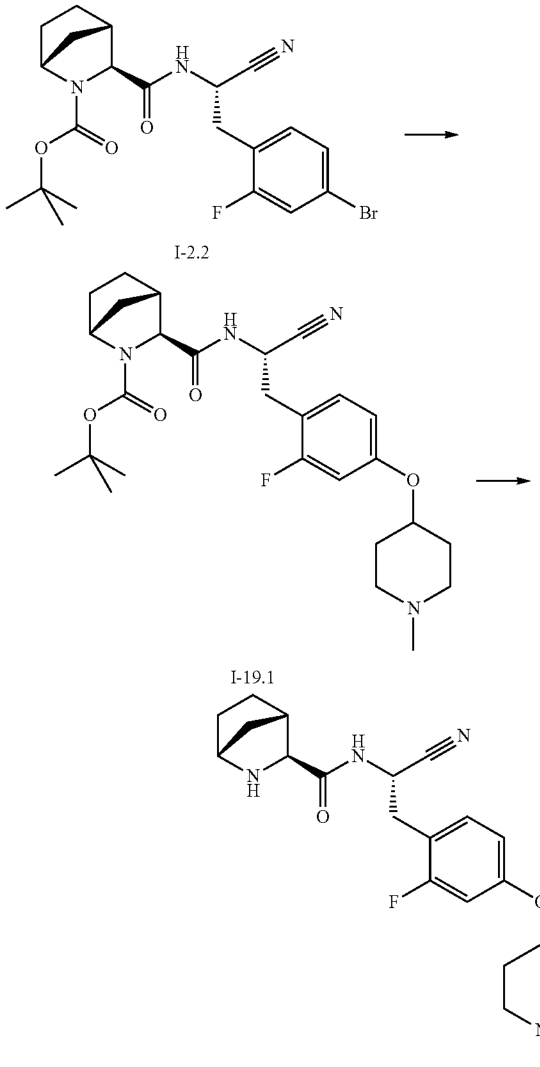
Step 6: Synthesis of Example 123 and 128

I-10.5 (48 mg, 0.09 mmol) is stirred in formic acid for 48 h. The mixture is purified by reversed phase HPLC. It is possible to separate the both isomers:

Isomer 1=example 123: yield 3%, m/z 387 [M+H]+, rt 0.38 min, LC-MS Method X012_S01,
Isomer 2=example 128: yield 6%, m/z 387 [M+H]+, rt 0.35 min, LC-MS Method X012_S01.
Method W

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[2-fluoro-4-[(1-methyl-4-piperidyl)oxy]phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 319



I-2.2

I-19.1

Example 319

Step 1: Synthesis of Intermediate I-19.1

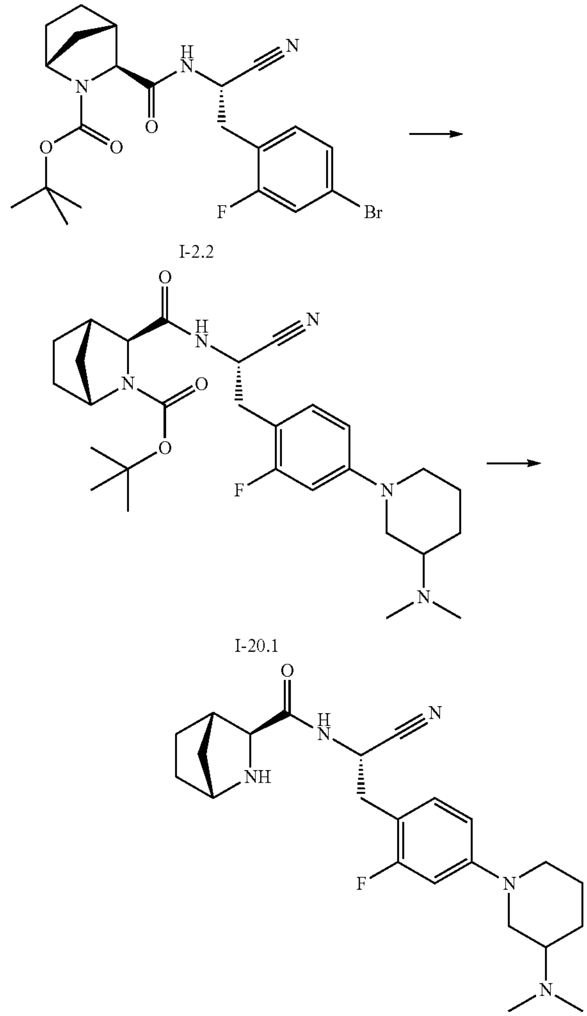
I-2.2 (300 mg, 0.64 mmol) in anhydrous toluene is purged with argon. 4-hydroxy-1-methylpiperidine (148.18 mg, 1.29 mmol), allylpalladium chloride dimer (5.88 mg, 0.016 mmol), 2-(di-t-butylphosphino)-3-methoxy-6-methyl-2'-4'-6'-tri-1-propyl-1,1'-biphenyl (18.09 mg, 0.039 mmol), cesium carbonate (314.4 mg, 0.965 mmol) and molecular sieve (4A) are added and purged with argon again. The reaction mixture is stirred at 90° C. for 21 h. Afterwards filtered through a pad of celite, washed with ethyl acetate and concentrated. The crude residue is purified by reversed phase HPLC and freeze dried. Yield 16%.

Step 2: Synthesis of Example 319
(See Method A2, Step 4)

To I-19.1 (50 mg, 0.1 mmol) in acetonitrile (6 mL) sodium iodide (45 mg, 0.3 mmol) and chlorotrimethylsilane (38.1 μL, 0.3 mmol) are added. The mixture is stirred for 2 h, then methanol is added, stirred for additional 30 min and then concentrated. The residue is purified by reversed phase HPLC. Yield 34%, m/z 401 [M+H]+, rt 0.31 min, LC-MS Method X012_S02.
Method W1

Synthesis of (1S,2S,4R)—N-[(1S)-1-cyano-2-[4-[3-(dimethylamino)-1-piperidyl]-2-fluoro-phenyl]ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

Example 344



I-2.2

I-20.1

Example 344

Step 1: Synthesis of Intermediate I-20.1

To I-2.2 (300 mg, 0.64 mmol) in anhydrous dioxane (8 mL) are added 3-dimethylamino-piperidine (164.96 mg, 1.29 mmol) and cesium carbonate (846.87 mg, 2.57 mmol). The mixture is purged with argon and chloro(2-dicyclohexylphosphino-2',4',6'-tri-1-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (95.05 mg, 0.13 mmol) is added and stirred at 90° C. for 2 h. The reaction mixture is filtered and concentrated. The residue is diluted with dichlormethane and water. The organic layer is separated, dried and concentrated. The crude product is purified by reversed phase HPLC. Yield 12%.

Step 2: Synthesis of Example 344

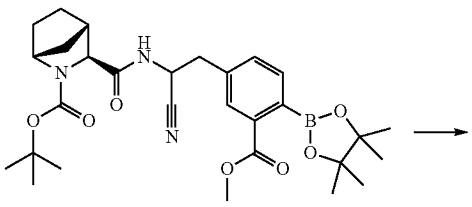
(See Method A5, Step 3)

To I-20.1 (53 mg, 0.1 mmol) in acetonitrile (8 mL) p-toluenesulfonic acid monohydrate (68.70 mg, 0.36 mmol) is added and stirred at r.t. for 6 h. The mixture is concentrated, diluted with methanol and purified by reversed phase HPLC. Yield 28%, m/z 414 [M+H]+, rt 0.74 min, LC-MS Method 004_CA05.

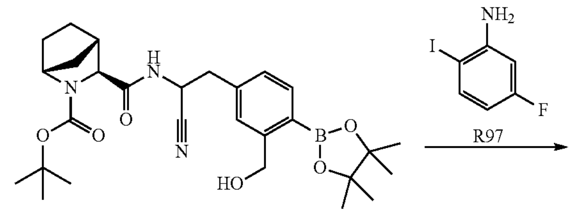
Method Z

Synthesis of (1S,2S,4R)—N-[1-cyano-2-(3-fluorophenanthridin-8-yl)ethyl]-3-azabicyclo[2.2.1]heptane-2-carboxamide

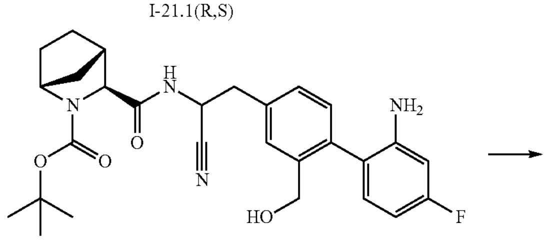
Example 315



I-18.1(R,S)

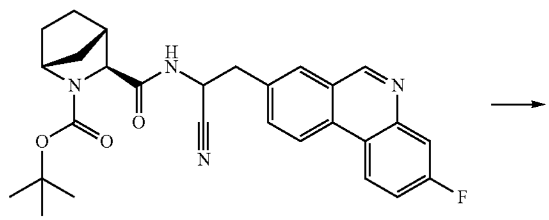


I-21.1(R,S)

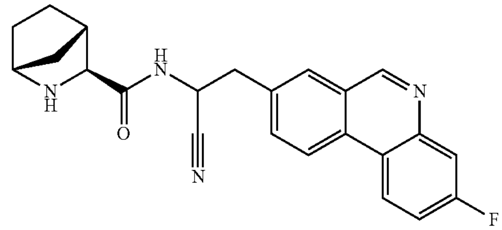


I-21.2(R,S)

-continued



I-21.3(R,S)



Example 315

Step 1: Synthesis of Intermediate I-21.1

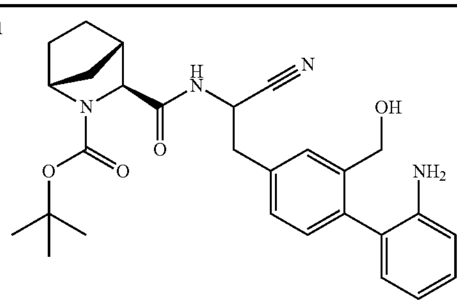
To I_18.1 (1.5 g, 2.7 mmol) in anhydrous THF (1 mL) under argon atmosphere lithium borhydride (59 mg, 2.7 mmol) is added. The mixture is heated to 50° C. overnight. The reaction mixture is carefully diluted with water and extracted with ethyl acetate. The organic layer is separated, dried and concentrated. The crude residue is filtered through a pad of silica gel (cyclohexane/ethyl acetate 1:2). Yield 37%.

Step 2: Synthesis of Intermediate I-21.2

To I-21.1 (260 mg, 0.495 mmol) in anhydrous ACN (5 mL) 5-fluoro-2-iodo-aniline (117.28 mg, 0.495 mmol), 1,1bis(diphenylphosphino)ferrocene palladium dichloride (36.21 mg, 0.049 mmol) and a solution of sodium carbonate in water 2 mol/L (0.742 mL, 1.48 mmol) are added and purged with argon and heated to 80° C. for 1 h. The reaction mixture is diluted with DCM and water. The organic layer is separated, dried and concentrated. The crude residue is purified by reversed phase HPLC. Yield 41%, m/z 509[M+H]+, rt 0.66 min, LC-MS Method X011_S03.

The following intermediate as shown in Table 36 is synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 36

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-21.2.1	I-21.1		491	0.63	X011_S03

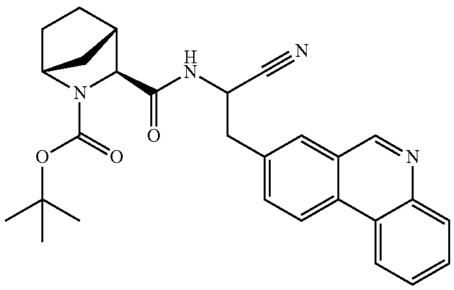
Step 3: Synthesis of Intermediate I-21.3

To I-21.2 (103 mg, 0.2 mmol) in DCM manganese(IV) oxide (153.65 mg, 8.73 mmol) is added under cooling. The reaction mixture is stirred at r.t. overnight and 1 h at 50° C. Another manganese(IV)oxide (50 mg, 2.84 mmol) is added and stirred for further 2 h at 50° C. The reaction mixture is filtered through a pad of cellulose and concentrated in vacuo. The residue is purified by reversed phase HPLC.

Yield 27%.

The following intermediate as shown in Table 37 is synthesized in a similar fashion from the appropriate intermediate ((R,S)=1:1 mixture of stereoisomers at the carbon adjacent to the nitrile group):

TABLE 37

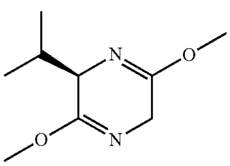
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-21.3.1	I-21.2.1		n.d.	n.d.	n.d.

Step 4: Synthesis of Example 315

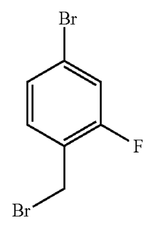
To I-21.3 (26.4 mg, 0.054 mmol) in acetonitrile, p-toluenesulfonic acid monohydrate (35.98 mg, 0.189 mmol) is added and stirred for 5 h. The reaction solution is purified by reversed phase HPLC. Yield 60%, m/z 389 [M+H]+, rt 0.37 min, LC-MS Method X12_S01.

Synthesis of Starting Materials/Educts

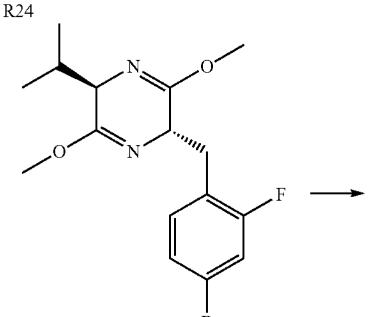
Synthesis of tert-butyl N-[(1S)-2-amino-1-[(4-bromo-2-fluoro-phenyl)methyl]-2-oxo-ethyl]carbamate (R1)



R24

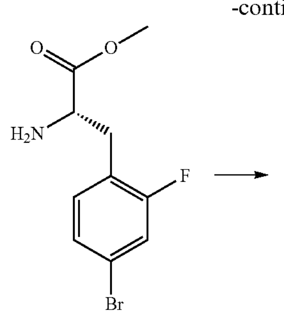


R25

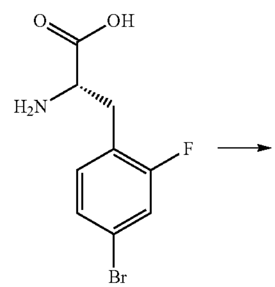


I-11.1

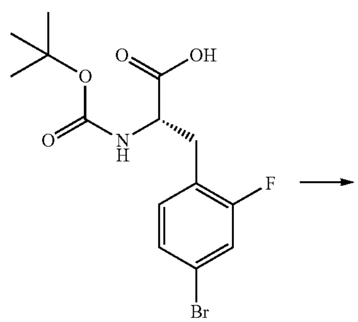
-continued



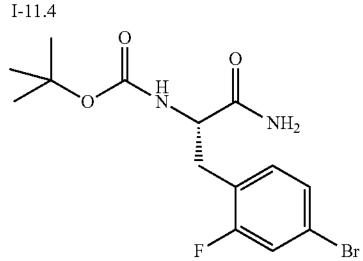
I-11.2



I-11.3



I-11.4



R1

Step 1: Synthesis of Intermediate I-11.1

R24 (212 g, 1151 mmol) in tetrahydrofuran (dry) (600 mL) is cooled to −78° C. Then n-butyllithium (2.5 M in hexanes, 552 mL, 1381 mmol) is added dropwise, keeping the temperature below −78° C. After 30 min R25 (324 g, 1209 mmol) in tertahydrofurane (dry) (120 mL) is added dropwise. The reaction mixture is stirred at −78° C. for 1 h. The mixture is quenched with saturated NH_4Cl solution and extracted three times with ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue is purified by flash chromatography (heptane/ethyl acetate=80/20). Yield 60%.

Step 2: Synthesis of Intermediate I-11.2

To I-11.1 (104 g, 265 mmol) in acetonitrile (600 mL) aq. 0.2 M HC (2788 mL, 558 mmol) is added.

The mixture is stirred at RT for 12 h. The mixture is extracted with diethylether and the pH of the aq. layer is adjusted to ~8 with sat. $NaHCO_3$-solution. Then it is extracted three times with ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4 and concentrated. Yield 80%.

Step 3: Synthesis of Intermediate I-11.3

I-11.2 (62.4 g, 211 mmol) is stirred in aq. 3 M HCl (3 mol/L, 1000 mL) at 60° C. for 16 h. The mixture is cooled down and the pH is adjusted to ~7 with aq. 6 M NaOH. Then the reaction mixture is filtered, washed three times with water and dried in a vacuum oven at 40° C. for 12 h. Yield 74%.

Step 4: Synthesis of Intermediate I-11.4

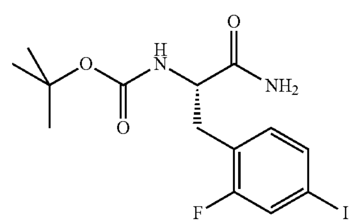
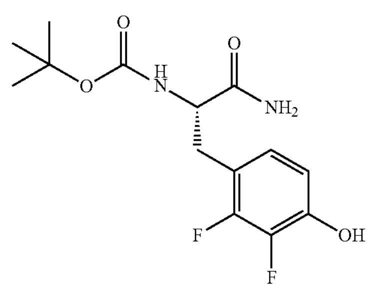
To I-11.3 (151 g, 546 mmol) in 1,4-dioxane (2.2 L) is added aq. 2 M sodium carbonate (301 mL) and di-tertbutyl dicarbonate (138 g, 147 mL). The mixture is stirred for 4 h. Then water is added and the pH is adjusted to ~4-5 with citric acid. The mixture is extracted three times with ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4 and concentrated. The residue is stirred in heptane for 15 min and the product is filtered off. Yield 87%.

Step 5: Synthesis of R1

To I-11.4 (181 g, 476 mmol) in dry DMF (1200 mL) N-methylmorpholine (72 g, 713 mmol) and TBTU (153 g, 476 mmol) are added and the reaction mixture is stirred for 30 min. Then the reaction mixture is cooled to 0° C. and aq. 35% ammonium chloride solution (47 mL, 856 mmol) is added and the mixture is stirred at room temperature for 12 h. Water is added and the formed product is filtered off and washed three times with water. The product is dried in a vacuum oven at 40° C. for 72 h. Yield 64%.

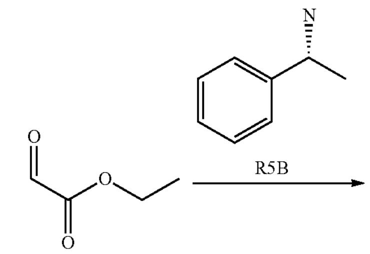
The following intermediate as shown in Table 38 is synthesized in a similar fashion from the appropriate intermediates:

TABLE 38

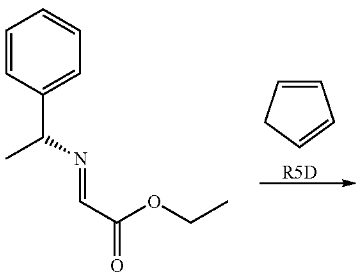
Intermediate	Structure	m/z [M + H]+	r (min)	LC-MS method
R1.1		409	1.05	V011_S01
R1.2		217 [M + H − BOC]+	0.69	Z018_S04

Synthesis of (1S,2S,4R)-3-[(tert.-butoxy)carbonyl]-3-azabicyclo[2.2.1]heptane-2-carboxylate (R5)

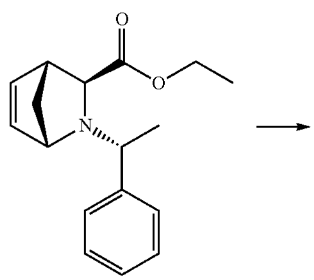
The compound is commercially available or can be synthesized in analogy to Tararov et al, Tetrahedron Asymmetry 13 (2002), 25-28.

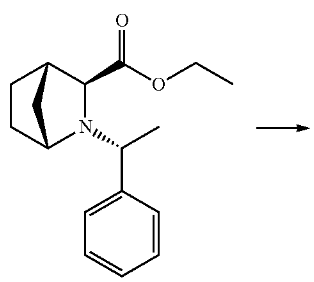


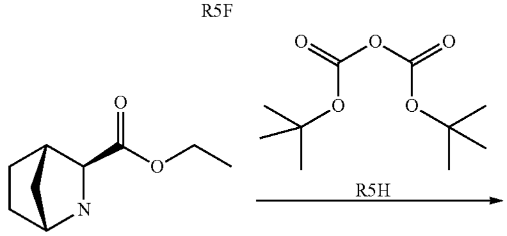
R5A



R5C

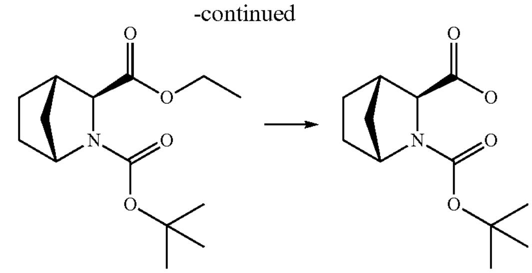

R5E


R5F



R5G

-continued


R5I R5

Step 1: Synthesis of R5C

A solution of R5A (44.9 g, 0.44 mol), freshly distilled from a commercially available solution in toluene (at 50 mbar, 55° C.) in diethylether (300 ml) is cooled at −10° C., followed by dropwise addition of R5B (53 g, 440 mmol), keeping the temperature below 0° C. After complete addition, MgSO4*H20 (91 g, 660 mmol) is added, and the resulting mixture stirred at room temperature overnight. The mixture is filtrated, the solution phase concentrated in vacuo and the residue distilled under reduced pressure to yield R5C (47 g, m/z 206 [M+H]+, rt 1.29 min, LC-MS Method V003_003). The product is used without further purification.

Step 2: A solution of R5C (47 g; 229 mmol) and R5D (30 g; 458 mmol) (freshly distilled from dicyclopentadien) in DMF (150 ml) and 120 μl water is cooled to 0° C., before TFA (18 ml; 234 mmol) is added dropwise. The mixture is stirred overnight at room temperature, then added to a solution of 40 g NaHCO3 in 1200 ml water and extracted with diethylether. The organic layer is separated, washed subsequently with aqueous NaHCO3 and water, dried over MgSO4, and concentrated in vacuo. The residue is worked up by column chromatography on silica (cyclohexane/ethyl acetate=9:1) to yield R5E (Yield 52% m/z 272 [M+H]+, rt 0.42 min, LC-MS Method X001_004)

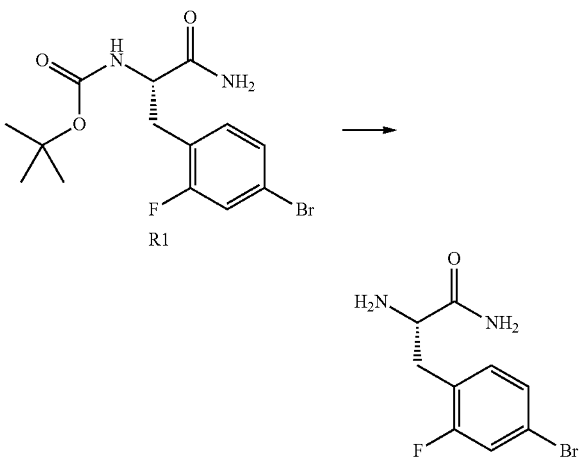
Step 3: To a solution of R5E (24.8 g, 91 mmol) in ethanol (250 ml), Raney-nickel is added (2.5 g) and reacted at 50 psi under a hydrogen atmosphere at room temperature. The catalyst is filtered of, the solution concentrated in vacuo and the residue worked up by chromatography on silica (cyclohexane/ethyl acetate 9:1). After evaporation of the organic solvent, the obtained product is redissolved in diethylether and triturated with solution of HCl in dioxane, concentrated in vacuo, redissolved in 200 ml ethanol and concentrated in vacuo to yield R5F: (Yield 78% m/z 274 [M+H]+, rt 0.42 min, LC-MS Method X001_004).

Step 4: To a solution of R5F (22 g, 71 mmol) in ethanol (250 ml), 10% Pd/C is added (2.5 g) and reacted at 15 bar under a hydrogen atmosphere at room temperature. The catalyst is filtered of, the solution concentrated in vacuo. The residue is washed with diisopropylether to yield R5G. (Yield 98% m/z 170 [M+H]+, rt 0.48 min, LC-MS Method V001_007).

Step 5: To R5G in a solution of triethylamin (24.6 ml), THF (150 ml) and water (2 ml), R5I (15.9 g; 73 mmol) is added and the resulting mixture stirred for 40 hours at room temperature, then concentrated in vacuo. Ethyl acetate is added to the residue, subsequently extracted with water, 1 N acidic acid and water, before the organic layer is dried over MgSO4 and concentrated in vacuo to yield R5I. (Yield 95% m/z 270 [M+H]+, rt 1.33 min, LC-MS Method V003_003).

Step 6: A mixture of R5I (16.9 g; 63 mmol) in acetone (152 ml), water (50 ml) and lithium hydroxide (3 g, 126 mmol) is stirred overnight at room temperature. Water (100 ml) was added, the volume reduced in vacuo before cooling to 0° C. followed by the addition of 1N aqueous HCl to acidify to a pH of 2-3, immediately followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO4$) and concentrated. To the residue, dichloromethane (100 ml) and cyclohexane (100 ml) was added, the volume reduced in vacuo by half and the mixture temperated at 15° C. The precipitate was filtered of, washed with cyclohexane to yield R5 (Yield 66%, m/z 242 [M+H]+).

Synthesis of (2S)-2-amino-3-(4-bromo-2-fluoro-phenyl)propanamide (R6)



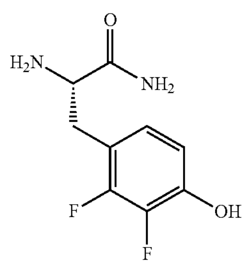
R1

R6

To R1 (10.0 g, 27.7 mmol) in DCM (70 mL) TFA (25 mL, 162.0 mmol) is added and the reaction mixture is stirred for 12 h. Then the reaction mixture is concentrated, the residue is dissolved in DCM and diisopropylether is added. The product precipitates and is filtered by suction and washed with diisopropylether. Yield >95% m/z 261 [M+H]+, rt 0.67 min, LC-MS Method V018_S01.

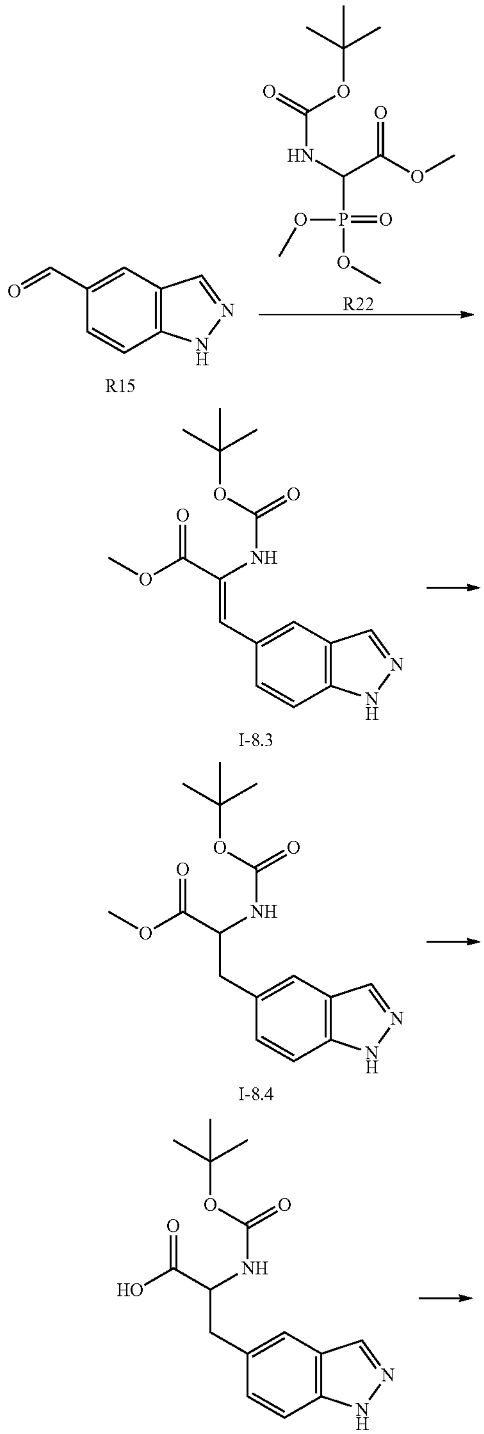
The following intermediate as shown in Table 38.1 is synthesized in a similar fashion from the appropriate intermediates:

TABLE 38.1

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R6.1		217	0.08	Z011_S03

For R6.1 the reaction time is 2 h. After the reaction mixture is concentrated, the crude residue is freeze-dried and used without further purification for the next step.

Synthesis of 2-Amino-3-(1H-indazol-5-yl)propanamide (R14)



R15

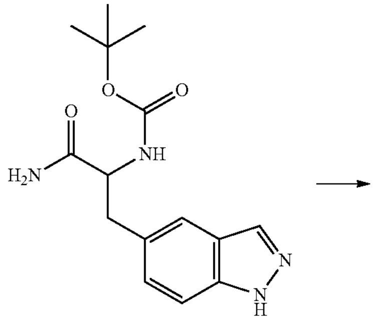
R22

I-8.3

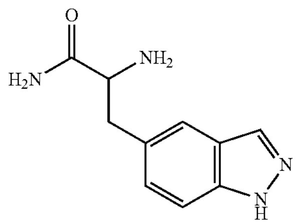
I-8.4

I-8.5

-continued



I-8.6



R14

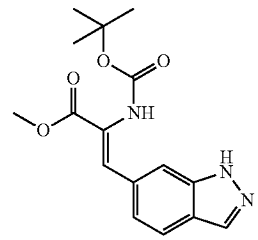
Step 1: Synthesis of Intermediate I-8.3

1,1,3,3-Tetramethylguanidin (0.44 mL, 3.51 mmol) in THF (5 mL) is cooled down to −70° C. Educt R22 (1.00 g, 3.36 mmol) is dissolved in 5 mL THF and is added. The mixture is stirred for 5 min before R15 (0.49 g, 3.36 mmol)—also dissolved in 5 mL THF—is added dropwise. The cooling is removed and the mixture warms up to room temperature. The reaction mixture is heated to 80° C. for 12 h. Because of remaining educt Tetramethylguanidin and R22 are added twice and the mixture is stirred at 80° C. for additional 4 h.

The reaction mixture is concentrated. Ethyl acetate and water are added to the residue. 1 M sulfuric acid is added and the organic layer is separated, is dried over $MgSO_4$ and concentrated. Yield 87%, m/z 318 [M+H]+, rt 0.97 min, LC-MS Method V011_S01.

The following intermediate as shown in Table 39 is synthesized in a similar fashion from the appropriate intermediate:

TABLE 39

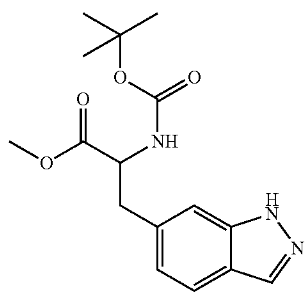
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-8.3.1		318	1.00	V012_S01

Step 2: Synthesis of Intermediate I-8.4

To I-8.3 (925 mg, 2.91 mmol) in methanol (30 mL) Pd/C (10%, 130 mg) is added. The reaction mixture is stirred under hydrogen (3 bar) for 16 h. Then the mixture is filtered and the filtrate is concentrated. The residue is triturated with diethyl ether and the product is filtered by suction. Yield 88%, m/z 320 [M+H]+, rt 0.99 min, LC-MS Method V011_S01.

The following intermediate as shown in Table 40 is synthesized in a similar fashion from the appropriate intermediate:

TABLE 40

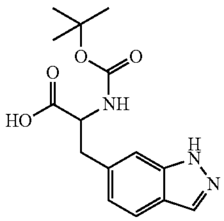
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-8.4.1	I-8.3.1		320	0.96	V011_S01

Step 3: Synthesis of Intermediate I-8.5

To I-8.4 (820 mg, 2.57 mmol) in methanol (15 mL) sodium hydroxide solution (2.5 mL, 1 mol/L) is added. The reaction mixture is heated to 40° C. for 2 h. The mixture is concentrated partially and 1 M HCl is added to neutralization. The precipitation is filtered with suction, is dissolved in methanol and concentrated quickly. Yield 65%, m/z 306 [M+H]+, rt 0.57 min, LC-MS Method V011_S01.

The following intermediate as shown in Table 41 is synthesized in a similar fashion from the appropriate intermediate:

TABLE 41

Intermediate	educt	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-8.5.1	I-8.4.1		306	0.55	V011_S01

Step 4: Synthesis of Intermediate I-8.6

To I-8.5 (400 mg, 1.31 mmol) in DMF (5 mL) diisopropylethylamine (502 μL, 2.88 mmol) and TBTU (421 mg, 1.31 mmol) are added and the reaction mixture is stirred for 15 min. Then aq. 30% ammonia solution (545 μL, 9.61 mmol) is added and the mixture is stirred for additional 12 h. Water is added to the reaction mixture and extracted with ethyl acetate. The organic layer is washed with brine and saturated $NaHCO_3$ solution, is dried over $MgSO_4$ and concentrated. Yield 55%, m/z 305 [M+H]+, rt 0.75 min, LC-MS Method V011_S01.

The following intermediate as shown in Table 42 is synthesized in a similar fashion from the appropriate intermediate:

For I-8.6.2 N-methylmorpholine is used instead of diisopropylethylamine (in analogy to synthesis of R1)

Step 5: Synthesis of R14

To I-8.6 (130 mg, 0.43 mmol) in DCM (3 mL) TFA (358 μL, 0.47 mmol) is added and the reaction mixture is heated to 30° C. for 12 h. Then the reaction mixture is concentrated. Yield >95%.

The following intermediate as shown in Table 43 is synthesized in a similar fashion from the appropriate intermediate:

TABLE 42

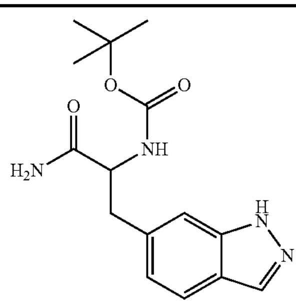
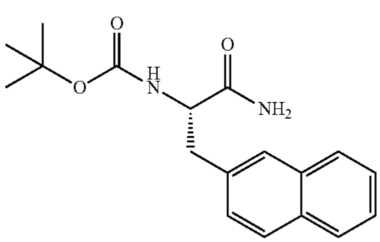
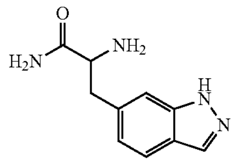
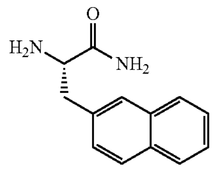
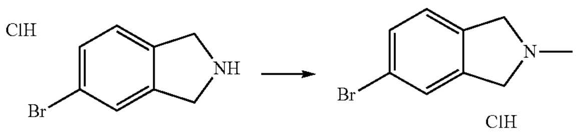
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
I-8.6.1	I-8.5.1		327 [M + Na]+	0.77	V011_S01
I-8.6.2	commerically available		315	n.d.	n.d.

TABLE 43

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
R14.1	I-8.6.1		227 [M + Na]+	0.53	V011_S01
R14.2	I-8.6.2		214	0.31	X012_S01

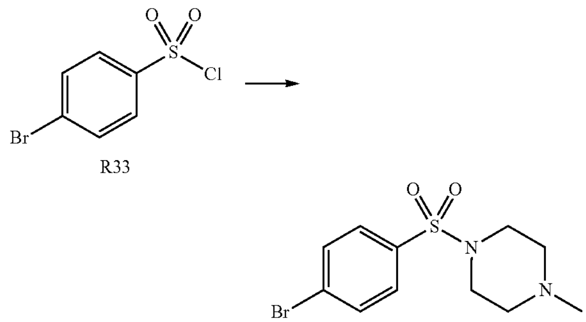
Synthesis of 5-bromo-2-methyl-isoindoline (R4)



R26 R4

The pH of a mixture of R26 (1.85 g, 7.9 mmol) in methanol (100 mL) and water (10 mL) is adjusted to ~5 with acetic acid. Then a 37% formalin solution (1.28 mL, 15.8 mmol) is added and the mixture is stirred for 15 min. Sodium cyanoborohydride (0.74 g, 11.8 mmol) is added and the reaction mixture is stirred for additional 12 h. The mixture is concentrated and ethyl acetate and aq. 1 M NaOH solution are added to the residue. The organic layer is washed with NaCl solution, dried over $MgSO_4$ and concentrated. The residue is dissolved in diethyl ether and ethereal HCl is added dropwise. The resulting precipitate is filtered off. Yield 62% m/z 212/214 [M+H]+, rt 0.65 min, LC-MS Method V012_S01.

Synthesis of 1-(4-bromo-benzenesulfonyl)-4-methyl-piperazine (R34)



R34

R33 (800 mg, 3.1 mmol) is dissolved in DCM, N-methylpiperazine (313 mg, 3.1 mmol) is added and stirred for 12 h. After addition of 2 mL 1N HCl under stirring the phases are separated. The organic phase is dried over $MgSO_4$ and after filtration evaporated in vacuo. Yield: 84% m/z 319 (M+H)+.

The following intermediates as shown in Table 44 are synthesized in a similar fashion from the appropriate intermediate:

TABLE 44

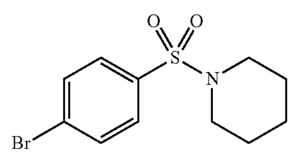
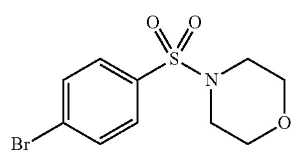
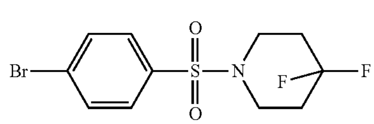
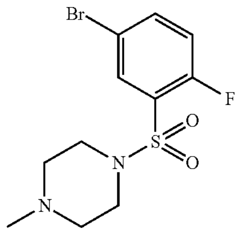
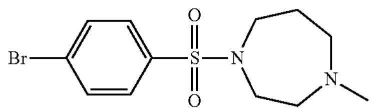
Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
R34.1	R33		304	n.d.	n.d.
R34.2	R33		306	n.d.	n.d.
R34.3	R33		340	0.64	X012_S01

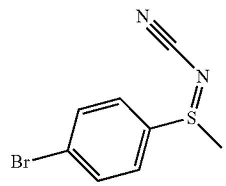
TABLE 44-continued

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
R34.4			337/339	0.36	X012_S01
R34.5			333/335	0.36	X012_S01

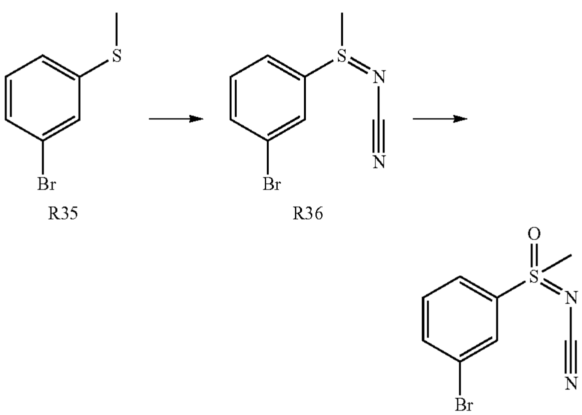
For R34.4 and R34.5 additional 2 eq. of DIPEA are added to the reaction mixture.

In analogy the following reagent as shown in Table 45 is prepared:

TABLE 45

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
R36.1	commerically available		243	0.64	Z018_S04

Synthesis of Reagent R37



R37

Step 1: Synthesis of R36

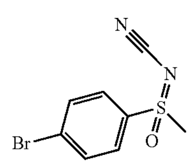
R35 (200 µL, 1.448 mmol) is dissolved in 10 mL methanol. Cyanamide (79.112 mg, 1.882 mmol), potassium tert-butoxide (194.9 mg, 1.737 mmol) and N-bromosuccinimide (386.282 mg, 2.171 mmol) are added and stirred for 1 h at room temperature. The product is purified by preparative HPLC (Waters 30×100 mm, 10 µm, sunfire RP18, acetonitrile/water/TFA). The fractions containing the product are combined and lyophilized. Yield 87%, m/z 244 [M+H]+, rt 0.62 min, LC-MS Method Z018_S04.

Step 2: Synthesis of R37

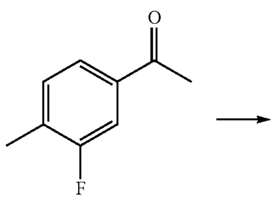
R36 (335 mg, 1.378 mmol) is dissolved in 3 mL ethanol. Potassium carbonate (571.315 mg, 4.134 mmol) and 3-chloroperbenzoic acid (356.696 mg, 2.067 mmol) are added at 0° C., and the mixture is stirred for 2 h at room temperature. The solvent is evaporated in vacuo and the residue is dissolved in DMF. The product is purified by preparative HPLC (Waters 30×100 mm, 10 µm, sunfire RP18, acetonitrile/water/TFA). The fractions containing the product are combined and lyophilized. Yield 71%, m/z 260 [M+H]+, rt 0.68 min, LC-MS Method Z018_S04.

In analogy the following reagent as shown in Table 46 is prepared:

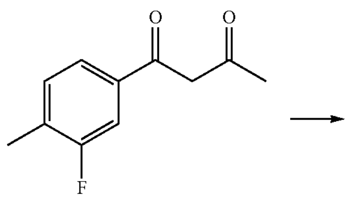
TABLE 46

Intermediate	Educt	Structure of Intermediate	m/z [M + H]+	rt (min)	LC-MS method
R37.1	R36.1		259	0.67	Z011_S03

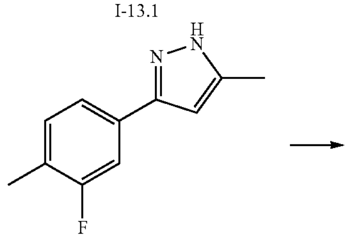
Synthesis of 1-[3-[4-(bromomethyl)-3-fluoro-phenyl]-5-methyl-pyrazol-1-yl]ethanone (R13)



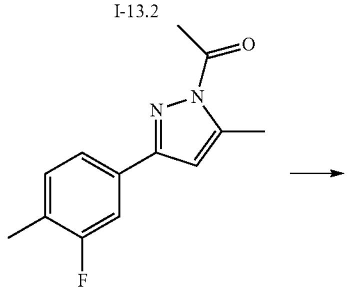
R28



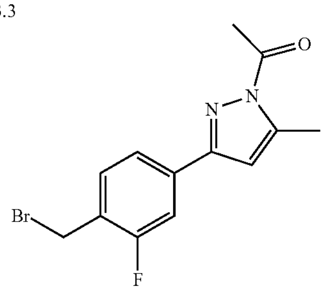
I-13.1



I-13.2



I-13.3



R13

Step 1: Synthesis of Intermediate I-13.1

To potassium tert.-butylate (7.4 g, 65.6 mmol) in anhydrous THF (300 mL) is added crown ether 18-6 (12.2 g, 46.0 mmol). The mixture is cooled down to 0° C. and R28 (5.0 g, 32.9 mmol) is added and stirred for 15 min at room temperature. Then acetic acid methyl ester (5.2 mL 65.7 mmol) is added and the reaction mixture is stirred for additional 1 h. The mixture is concentrated and the residue is purified via flash chromatography (cyclohexane/ethyl acetate=95:5). Yield 79%, m/z 195 [M+H]+, rt 0.66 min, LC-MS Method V011_S01.

Step 2: Synthesis of Intermediate I-13.2

To I-13.1 (5.1 g, 26.1 mmol) 1 M hydrazine solution in THF (78.2 mL, 78.2 mmol) is added and the reaction mixture is heated to 80° C. for 12 h. The reaction mixture is concentrated and the residue is purified via flash chromatography (cyclohexane/ethyl acetate=70:30). Yield 90%, m/z 191 [M+H]+, rt 1.01 min, LC-MS Method V011_S01.

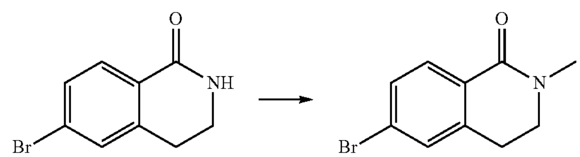
Step 3: Synthesis of Intermediate I-13.3

I-13.2 (1.00 g, 5.3 mmol) and acetic acid anhydride (5.00 mL, 53.0 mmol) are stirred for 12 h. Water and methanol are added to the reaction mixture, the precipitate is filtered by suction and dried in vacuo. Yield 87%, m/z 233 [M+H]+, rt 1.31 min, LC-MS Method V011_S01.

Step 4: Synthesis of R13

To I-13.3 (0.95 g, 4.1 mmol) in DCM (25 mL) is added N-bromo succinimide (0.80 g, 4.5 mmol) and 2,2'-azobis (isobutyronitrile) (50 mg). The reaction mixture is refluxed for 12 h under radiation with an Hg lamp. The mixture is concentrated and the residue is purified via flash chromatography (cyclohexane/DCM=75:25). Yield 39%, m/z 311 [M+H]+, rt 1.43 min, LC-MS Method V018_S01.

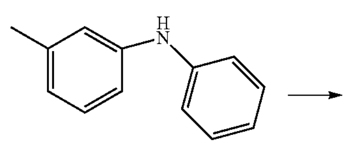
Synthesis of 6-bromo-2-methyl-3,4-dihydroisoquinolin-1-one (R32)



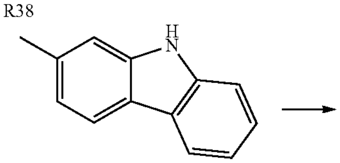
R31 R32

R31 (500 mg, 2.2 mmol) in DMF (3 mL) is cooled down to 0° C. Under argon atmosphere NaH (60%, 121 mg, 3.0 mmol) is added and stirred for 20 min. Then methyl iodide (0.275 mL, 4.4 mmol) is added and the mixture is stirred for additional 1 h at 0° C. Ice water is added to the reaction mixture and the precipitate is filtered by suction and dried at 50° C. in the vacuum oven for 12 h. Yield 73%, m/z 240/242 [M+H]+, rt 0.89 min, LC-MS Method V012_S01.

Synthesis of tert-butyl 2-(bromomethyl)-9H-carbazole-9-carboxylate (R13.1 for synthesis of I-7.1.3)

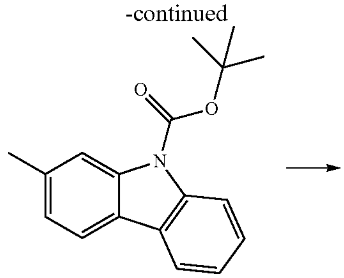


R38

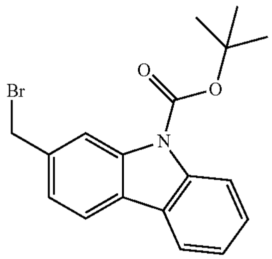


I-15.1

-continued



I-15.2



R13.1

Step 1: Synthesis of Intermediate I-15.1

3-Methyl-diphenylamine R38 (1.0 g, 5.5 mmol), K_2CO_3 (75 mg, 0.55 mmol) and palladium acetate (37 mg, 0.16 mmol) in 2,2-dimethyl-1-propanol (5 mL) is stirred at 110° C. for 14 h. Water is added to the reaction mixture and extracted with dichloromethane. The combined organic layer is concentrated in vacuo, residue triturated with methanol/dichloromethane and dried in vacuo and directly taken to the next step. Yield 29%, m/z 182 [M+H]+, rt 0.67 min, LC-MS Method X012_S01.

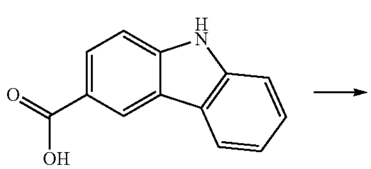
Step 2: Synthesis of Intermediate I-15.2

I-15.1 (285 mg, 1.6 mmol), di-tert.-butyl dicarbonate (412 mg, 1.9 mmol) and DMAP (50 mg, 0.41 mmol) in dichloromethane (10 ml) are stirred at room temperature for 16 hours. The reaction mixture extracted with water, the organic layer is separated and concentrated in vacuo and directly taken to the next step. Yield 86%, m/z 282 [M+H]+, rt 0.89 min, LC-MS Method X012_S01.

Step 3: Synthesis of Intermediate R13.1

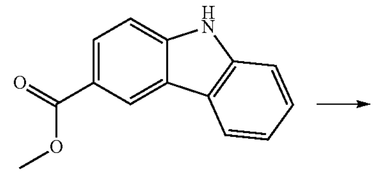
I-15.2 (380 mg, 1.4 mmol), N-bromosuccinimide (289 mg, 1.6 mmol), AIBN (20 mg, 0.12 mmol) in tetrachloromethane (5 mL) is heated to reflux over 16 h. Water and dichloromethane are added to the reaction mixture, the organic layer separated and concentrated. The residue is triturated with methanol and used directly in the next step. Yield 41%, m/z 360 [M+H]+, rt 0.67 min, LC-MS Method V0110_S01.

Synthesis of tert-butyl 3-(chloromethyl)-9H-carbazole-9-carboxylat (R13.2 for synthesis of I-7.1.6)

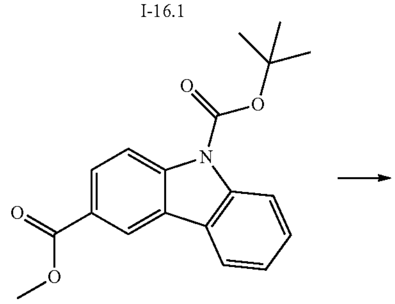


R39

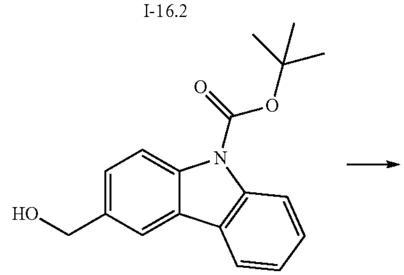
-continued



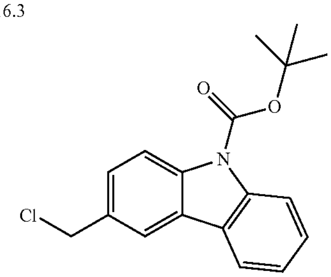
I-16.1



I-16.2



I-16.3



R13.2

Step 1: Synthesis of Intermediate I-16.1

9H-Carbazole-3-carboxylic acid R39 (500 mg, 2.4 mmol), in methanol (20 mL) is cooled to 0° C. Thionylchloride (206 ml, 2.8 mmol) is added dropwise to the stirred mixture at this temperature. The mixture is then stirred at room temperature for 16 hours. The formed precipitate is filtered and dried in vacuo and directly taken to the next step. Yield 53%, m/z 226 [M+H]+, rt 0.59 min, LC-MS Method X012_S01.

Step 2: Synthesis of Intermediate I-16.2

I-16.1 (280 mg, 1.2 mmol), di-tert.-butyl dicarbonate (326 mg, 1.5 mmol) and DMAP (50 mg, 0.41 mmol) in dichloromethane (10 ml) are stirred at room temperature for 16 hours. The reaction mixture extracted with water, the organic layer is separated and concentrated in vacuo and directly taken to the next step. Yield 99%, m/z 326 [M+H]+, rt 0.84 min, LC-MS Method X012_S01.

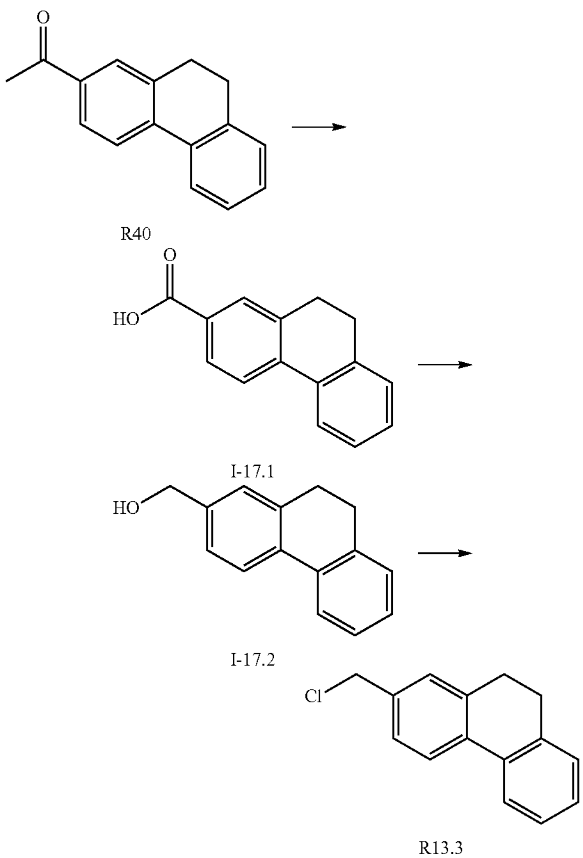
Step 3: Synthesis of Intermediate I-16.3

I-16.2 (400 mg, 1.2 mmol) and boronhydride-tetrahydrofuran addukt (1.2 ml 1M in THF, 1.2 mmol) are dissolved in THF (5 ml). LiBH4 is repeatedly added in small portions at 50° C., until HPLC shows completion of reaction. Water and dichloromethane are added to the reaction mixture, the organic layer separated, concentrated. and purified via HPLC. Yield 40%, m/z 280 [M−H2O+H]+, rt 0.70 min, LC-MS Method X012_S01.

Step 4: Synthesis of Intermediate R13.2

I-16.3 (145 mg, 0.5 mmol) and DIPEA (171 μl, 1.0 mmol) are dissolved in dichloromethane (10 ml) and cooled to −10° C. Methanesulfonylchloride (46 μl, 0.6 mmol) in dichloromethane (1 ml) is added dropwise. After complete addition, the mixture is stirred for 16 h at room temperature. Water is added to the reaction mixture, the organic layer separated, concentrated in vacuo to yield R13.2, which is directly taken to the next step. Yield 73%, rt 0.87 min, LC-MS Method X012_S01.

Synthesis of 2-(chloromethyl)-9,10-dihydrophenanthrene (R13.3 for synthesis of I-7.1.4)



Step 1: Synthesis of Intermediate I-17.1

2-Acetyl-9,10-dihydro-phenanthren R40 (1.0 g, 4.5 mmol) is added to solution of bromine (924.7 μl, 18 mmol) and KOH (3.3 g, 58.5 mmol) in water (20 ml) at 0° C. After addition is completed, the reaction mixture is heated to 55° C. for 16 hours. The mixture is cooled to r.t., extracted with dichloromethane. The aqueous phase is separated, acidified with 1 M HCl aq and the precipitating product is filtered off and dried in vacuo at 50° C. Yield 92%, m/z 225 [M+H]+, rt 0.62 min, LC-MS Method X012_S01.

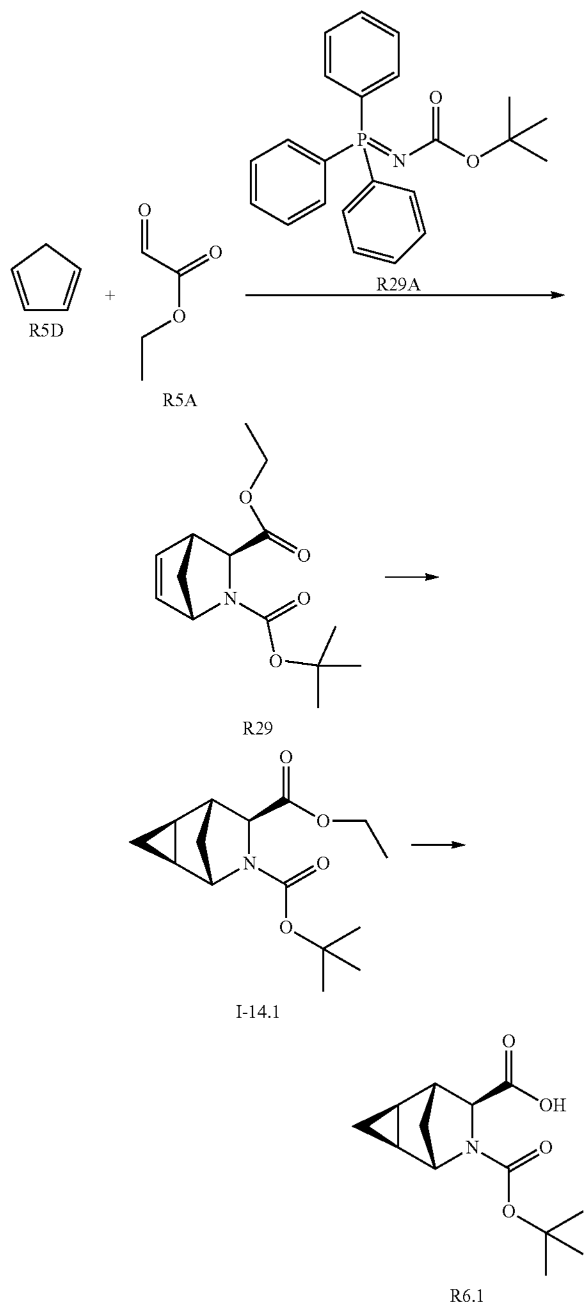
Step 2: Synthesis of Intermediate I-17.2

I-17.1 (930 mg, 4.2 mmol) is dissolved in THF (10 ml), CDI (874 mg, 5.4 mmol) is added in small portions and the mixture is stirred for 1 h at 50° C. The mixture is added slowly to sodium borohydride (470 mg, 12.4 mmol) in ice water, so that the temperature remains below 10° C. The mixture is stirred for 16 hours at r.t. and extracted with dichloromethane/water. The organic layer is separated and concentrated in vacuo, the remaining crude product purified via HPLC. Yield 53%, m/z 210 [M]+, 193 [M−H_2O]+, rt 0.61 min, LC-MS Method X012_S01.

Step 3: Synthesis of Intermediate R13.3

I-17.2 (460 mg, 2.2 mmol), DIPEA (766 μl, 4.4 mmol) are dissolved in dichloromethane (10 ml) and cooled to −10° C. Methanesulfonylchloride (207 μl, 2.6 mmol) in dichloromethane (1 ml) is added dropwise. After complete addition, the mixture is stirred for 16 h at room temperature. Water is added to the reaction mixture, the organic layer separated, concentrated in vacuo and the remaining crude product purified via HPLC. Yield 67%, m/z 228 [M]+, rt 0.79 min, LC-MS Method X012_S01.

Synthesis of 6-Aza-tricyclo[3.2.1.0*2,4*]octane-6,7-dicarboxylic acid 6-tert-butylester (R6.2)



Step 1: Synthesis of Intermediate R29.2

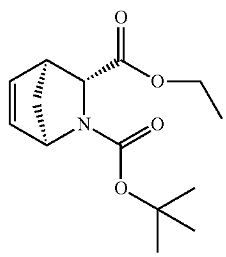
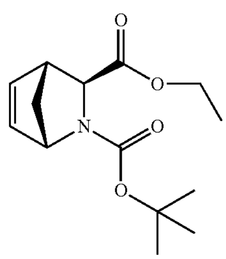
Dicyclopenta-1,3-diene is cracked and distilled at 42° C. and 1013 mbar to give cyclopenta-1,3-diene.

Ethyl 2-oxoacetate is also freshly distilled from a commercially available solution in toluene. Assumed concentration is 50%.

To N-boc-imino-(triphenyl)phosphorane (11.32 g, 30.00 mmol) in toluene (100 mL) is added ethyl 2-oxoacetate (15 mL, 60.00 mmol) and cyclopenta-1,3-diene (5 mL, 60.00 mmol) and stirred overnight at r.t. The reaction mixture is concentrated and the crude residue is purified over silica gel (cyclohexane/ethyl acetate 7:3). Yield 16%

R29.2. can be obtained through preparative chiral chromatography from this mixture of R29.1 and R29.2 (table 46.1) using method Chiral SFC G

TABLE 46.1

Intermediate	Structure of Intermediate
R29.1	
R29.2	

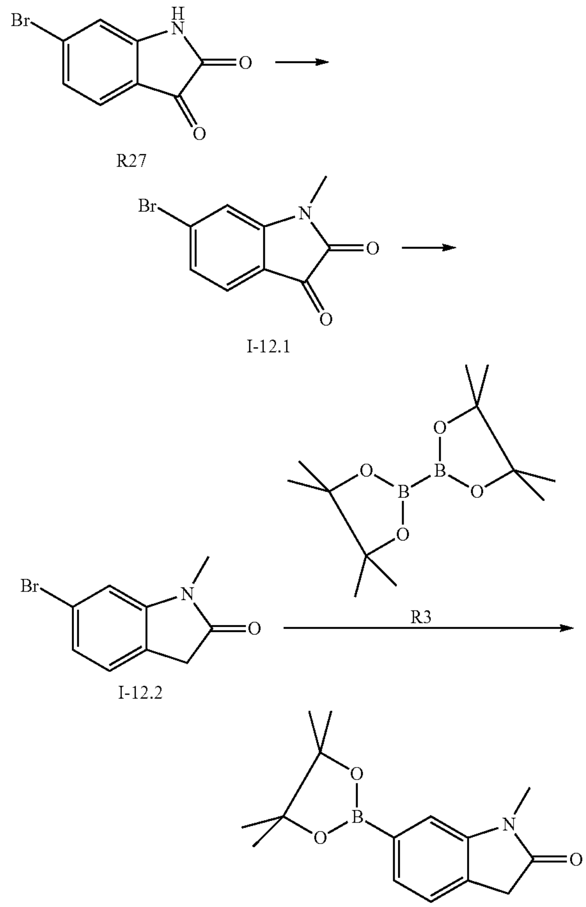
Step 2: Synthesis of Intermediate I-14.1

To R29.2 (5.00 g, 18.7 mmol) in diethylether (100 mL) is added palladium(II) acetate (0.42 g, 1.87 mmol). Under stirring diazomethane solution in diethylether (62 mmol) is added. The reaction mixture is stirred for 12 h. To destroy remaining diazomethane, silica gel and 3 mL acetic acid are added. Then the mixture is stirred for additional 1 h and filtrated. The solution is concentrated and extracted with DCM, water and brine. Yield 98%, m/z 226 [M+H−tButyl]+, rt 0.64 min, LC-MS Method X012_S01.

Step 3: Synthesis of R6.2

To I-14.1 (5.40 g, 19.2 mmol) in dioxane (60 mL) is added aq. 4 M NaOH (20 mL, 80 mmol). The reaction mixture is heated to 50° C. for 3 h. The mixture is extracted two times with DCM, then the water layer neutralized with 2 M HCl and extracted three times with DCM. The combined organic layers are dried over $MgSO_4$ and concentrated. The residue is dissolved in diethylether and evaporated, the product crystallizes. Yield 88%, m/z 198 [M+H−tButyl]+, rt 0.48 min, LC-MS Method X012_S01.

Synthesis of 1-Methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-indol-2-one (R7)



Step 1: Synthesis of Intermediate I-12.1

To R27 (25.0 g, 111 mmol) in acetonitrile (750 mL) is added MeI (15 mL, 241 mmol) and K_2CO_3 (60.0 g, 434 mmol) and the reaction mixture is stirred at 60° C. for 2 h. The reaction mixture is filtered and concentrated. Water and ethyl acetate are added to the residue. The organic layer is extracted twice with water, dried over $MgSO_4$ and concentrated. Yield 56%, m/z 240/242 [M+H]+, rt 0.48 min, LC-MS Method X001_004.

The following intermediates as shown in Table 47 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 47

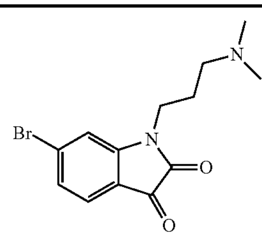
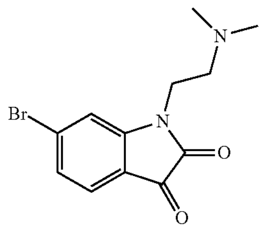
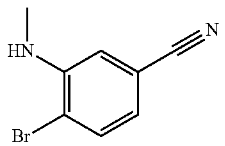
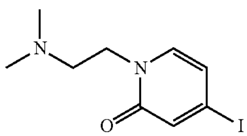
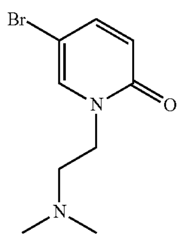
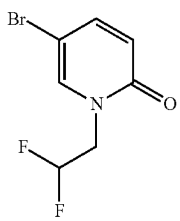
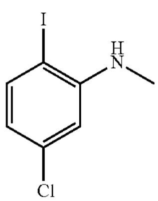
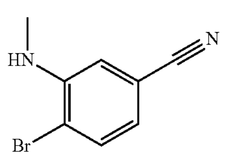
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-12.1.1		311/313	0.362	Z020_S01

TABLE 47-continued

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-12.1.2		n.d.	n.d.	n.d.
I-12.1.3		211/213	0.55	X012_S01
I-12.1.4		n.d.	n.d.	n.d.
I-12.1.5		245	0.21	X012_S01
I.12.1.6		n.d.	n.d.	n.d.
I-12.1.7		268	0.71	X012_S01
I-12.1.8		211/213	0.55	X012_S01

For I-12.1.1, I-12.1.2, I-12.1.3, I-12.1.5, I-12.1.7 and I-12.1.8 sodium hydride and DMF is used instead of potassium carbonate and ACN.

For I-12.1.3, I-12.1.7 and I-12.1.8 the reaction temperature is r.t.

For I-12.1.4 DMF is used.

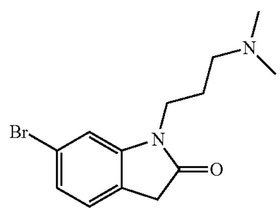
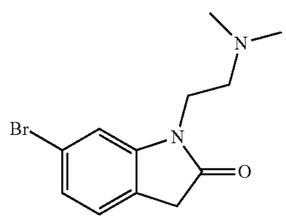
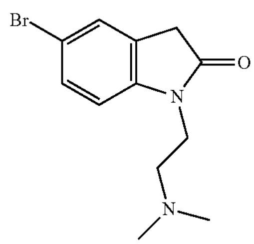
For I-12.1.6 the reaction conditions differ: 1,1-Difluoro-2-trifluoromethanesulfonyl-ethane is used as alkylation reagent in triethylamin as solvent at r.t.

Step 2: Synthesis of Intermediate I-12.2

I-12.1 (15.0 g, 63 mmol) and hydrazine hydrate (30 mL, 618 mmol) are heated to 125° C. for 72 h. To the cool reaction mixture DCM is added and extracted with water and 1 M HCl. The organic layer is dried over $MgSO_4$ and concentrated. The crystallized residue is dissolved in DCM, methanol is added and the DCM is removed in vacuo. The crystallized product is filtered by suction and washed with cold methanol. Yield 63%, m/z 226/228 [M+H]+, rt 1.16 min, LC-MS Method V001_003.

The following intermediates as shown in Table 48 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 48

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-12.2.1		n.d.	n.d.	n.d.
I-12.2.2		283/285	0.832	n.d.
I-12.2.3		n.d.	n.d.	n.d.

Step 3: Synthesis of Intermediate R7

To I-12.2 (32.0 g, 142 mmol) in anhydrous dioxane (400 mL) is added R3 (54.4 g, 241 mmol) and potassium acetate (41.6 g, 424 mmol). The mixture is purged with Argon, [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) as a complex with dichloromethane (11.2 g, 14 mmol) is added and the mixture is heated to 90° C. for 2 h. The reaction mixture is diluted with ethyl acetate and water, the organic layer is washed with water, dried over $MgSO_4$ and concentrated. The residue is purified via flash chromatography (cyclohexane/EA=70:30). Yield 72%, m/z 274 [M+H]+, rt 0.67 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 49 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 49

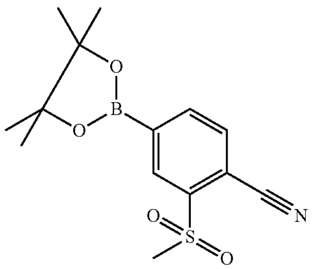
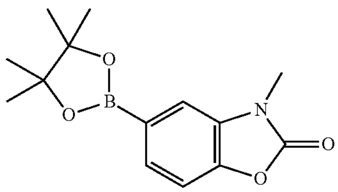
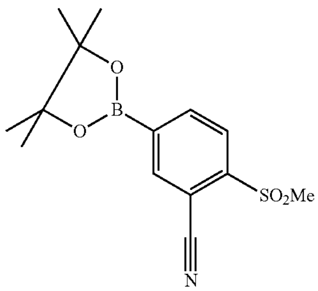
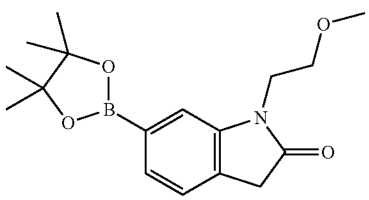
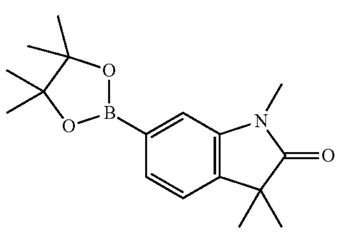
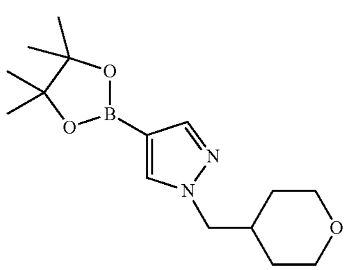
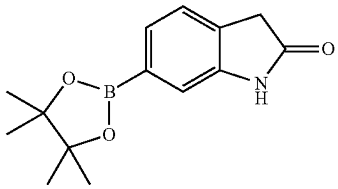
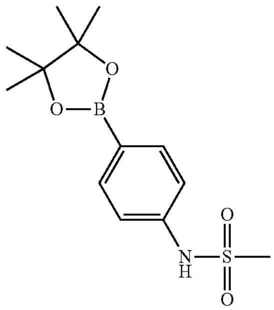
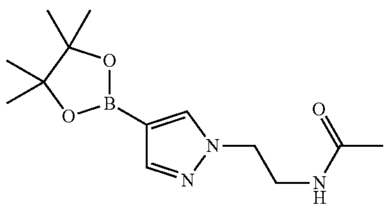
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R7.1		325 $[M + NH_4]+$	0.30	X018_S01
R7.2		276 [M + H]+	0.94	X002_002
R7.3		n.d.	n.d.	n.d.
R7.4		318	0.92	Z018_S04
R7.5		302	n.d.	n.d.
R7.6		294	0.85	Z018_S04

TABLE 49-continued

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R7.7		260	0.65	X001_004
R7.8		n.d.	n.d.	n.d.
R7.9		280	0.63	X001_002

Synthesis of Boronic Ester R7.6

2 g (10.3 mmol) 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 2.9 mL (20.6 mmol) 4-(iodomethyl)-tetrahydro-2H-pyran are dissolved in 200 mL DMF and 4.274 g (30.9 mmol) K_2CO_3 are added. The mixture is shaken at 80° C. for 5 h. After cooling to r.t. the mixture is filtered, the filtrate is concentrated in vacuo to approximately 60 mL. The product is separated using HPLC-MS (Gilson, mass flow 120 mL/min, 10 μm, 200 g Sunfire RP18, ACN/water/TFA). The product fractions are combined and freeze-dried to yield 115 mg product (3.8%) R7.6.

Synthesis of Boronic Ester R7.8

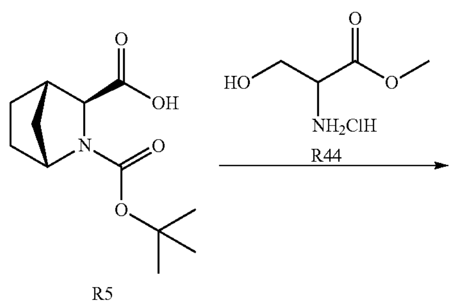
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 g, 4.56 mmol) and pyridine (10 mL) are cooled down with an ice bath. Methanesulfonyl chloride (0.933 mL, 12.01 mmol) is dissolved in dichlormethane (10 mL) and added slowly dropwise. The reaction mixture is allowed to come to room temperature and concentrated. The residue is diluted with dichlormethane and water. The organic layer is separated, dried and concentrated. The crude product is used without further purification. Yield: >95%

Synthesis of Boronic Ester R7.9

Under nitrogen atmosphere to sodiumhydride (50%) (0.218 g, 4.54 mmol) and DMF (3 mL) is added 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.5 g, 2.5 mmol) and stirred for 30 min at r.t. N-(2-chloroethyl) acetamide (0.775 mL, 7.52 mmol) is added and stirred at 90° C. overnight. Due to no reaction N-(2-chloroethyl)acetamide (0.26 mL) and copper(I)iodide (25 mg, 0.13 mmol) are added and stirred at 90° C. for 24 h. The reaction mixture is diluted with methanol, filtered through a thiol cartridge and concentrated. The crude product is used without further purification. Yield: 100%

All other boronic acid derivatives R9 and R16 and alkynes R10 are purchased or prepared by literature known procedures.

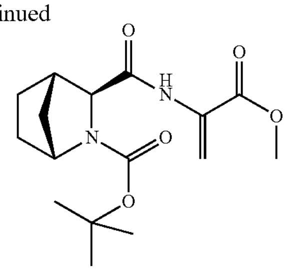
Synthesis of tert-butyl (1S,2S,4R)-2-(1-methoxycarbonylvinylcarbamoyl)-3-azabicyclo[2.2.1]heptane-3-carboxylate (R41)



R5

I-22.1

-continued



R41

Step 1: Synthesis of Intermediate I-22.1

To R5 (500 mg, 2.07 mmol) in DMF (5 mL) are added HATU (866.72 mg, 2.28 mmol) and DIPEA (1.43 mL, 8.29 mmol) and stirred at r.t. for 15 min. To the reaction mixture is added methyl 2-amino-3-hydroxy-propanoate hydrochloride (354.64 mg, 2.28 mmol) and stirred at r.t. for 4 h. The reaction mixture is diluted with ACN and water and purified by reversed phase HPLC.

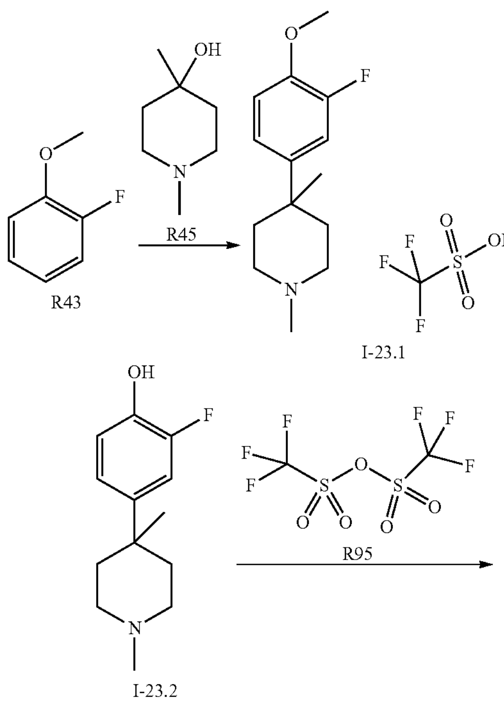
Yield 79%, m/z 343 [M+H]+, rt 0.44 min, LC-MS Method X011_S03.

Step 2: Synthesis of R41

I-22.1 (100 mg, 0.29 mmol) is dissolved in dichlormethane (2 mL) and cooled down to 0° C. 4-dimethylamino pyridine (1.78 mg, 0.015 mmol), TEA (65.13 μL, 0.47 mmol) and methansulfonyl chloride (29.59 μL, 0.38 mmol) are added and stirred at r.t. for 3 h. The reaction mixture is diluted with sodium carbonate solution. The organic layer is separated, dried and concentrated. The crude residue is purified by reversed phase HPLC.

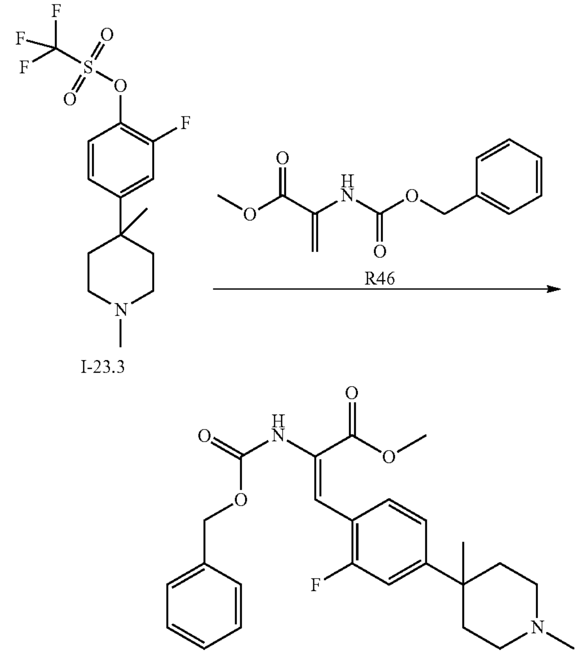
Yield 27%, m/z 324 [M+H]+, rt 0.63 min, LC-MS Method X011_S03.

Synthesis of methyl(E)-2-(benzyloxycarbonylamino)-3-[4-(1,4-dimethyl-4-piperidyl)-2-fluorophenyl]prop-2-enoate (R42)



R43 R45 I-23.1 I-23.2 R95

-continued



I-23.3 R46

R42

Step 1: Synthesis of Intermediate I-23.1

To 1-fluoro-2-methoxy-benzene (25 mL, 222.79 mmol) and 1,4-dimethylpiperidin-4-ol (7 g, 54.18 mmol) is added trifluoromethanesulfonic acid (50 mL, 565.04 mmol) under ice bath cooling. The reaction mixture is stirred at r.t. overnight, poured into iced water and extracted with PE. To the aqueous phase is added solid sodium carbonate and extracted with ethyl acetate. The organic layer is dried and concentrated. The crude product is triturated with diisopropylether and the precipitate is filtered off. Yield 82%, m/z 238 [M+H]+, rt 0.39 min, LC-MS Method X018_S02.

Step 2: Synthesis of Intermediate I-23.2

To I-23.1 (16.9 g, 43.63 mmol) in dichlormethane (150 mL) is added boron tribromide 1M in dichlormethane (44 mL, 44 mmol) and stirred at r.t. overnight. The reaction mixture is diluted with dichlormethane and 10% K_2CO_3-solution. The resulting precipitate is filtered off. The aq. layer is repeatedly extracted with dichlormethane, the precipitate formed upon standing at rt is filtered off and washed with dichlormethane. The dichloromethane phase is concentrated and purified by reversed HPLC and freeze dried. The isolated precipitates and the corresponding HPLC fractions are combined to yield the desired product.

Yield 18%, m/z 224 [M+H]+, rt 0.61 min, LC-MS Method V011_S01.

Step 3: Synthesis of Intermediate I-23.3

To I-23.2 (1.4 g, 6.27 mmol) in anhydrous dichlormethane (40 mL) triethylamine (1.8 mL, 12.985 mmol) is added and cooled down to −20° C. Trifluoromethanesulfonic acid anhydride (1.1 mL, 6.538 mmol) is added dropwise and stirred at −10° C. for 30 min. The reaction mixture is diluted with dichlormethane, washed with K_2CO_3-solution and brine. The organic layer is dried and concentrated. The crude product is used for the next step without further purification. Yield 98%, m/z 356 [M+H]+, rt 1.30 min, LC-MS Method V011_S01.

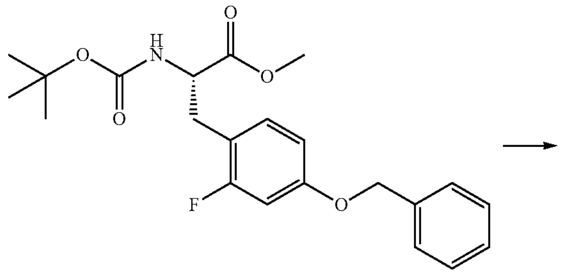
Step 4: Synthesis of R42

2-benzyloxycarbonylamino-acrylicacidmethylester (2.274 g, 9.67 mmol), bis(dibenzylideneacetone) palladium (0) (295 mg, 0.32 mmol), (2-biphenylyl)di-tert-butylphosphine (345 mg, 1.156 mmol) and lithium chloride (710 mg, 16.73 mmol) are purged with argon. I-23.3 (2.29 g, 6.44 mmol) dissolved in DMF (15 mL) and triethylamine are added and stirred at 80° C. overnight. The reaction mixture is concentrated, then diluted with dichlormethane and washed with 5% K_2CO_3-solution. The organic layer is dried and concentrated. The crude product is purified by reversed phase HPLC.

Yield 33%, m/z 441 [M+H]+, rt 1.23 min, LC-MS Method V011_S01.

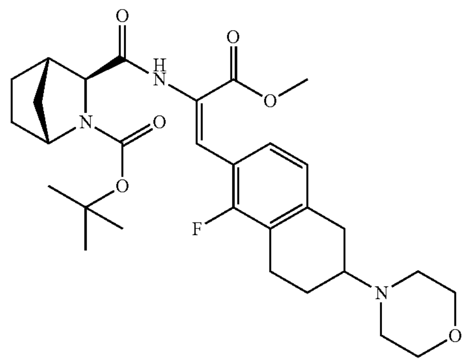
The following intermediate as shown in Table 50 is synthesized in an analogous manner from the appropriate intermediate R41 and R91:

-continued

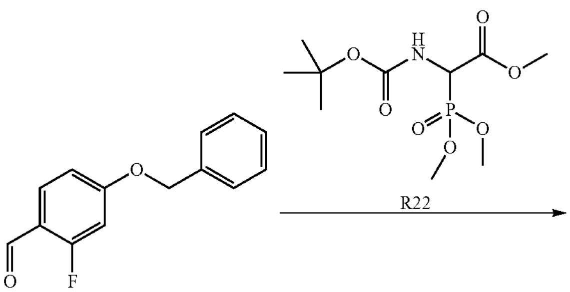


I-24.2

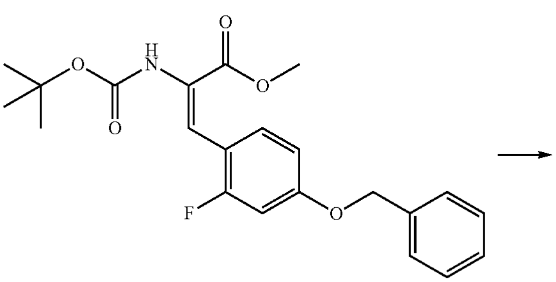
TABLE 50

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R42.1		558	0.47	X018_S01

Synthesis of (2S)-2-amino-3-(4-benzyloxy-2-fluoro-phenyl)propanamide hydrochloride (R47)

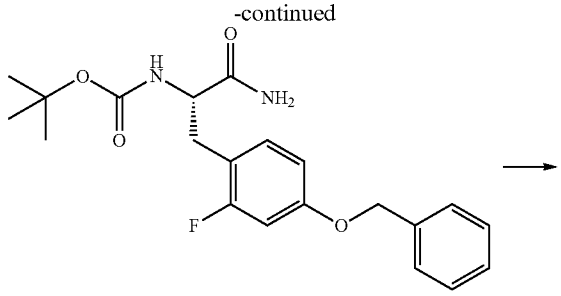


R48

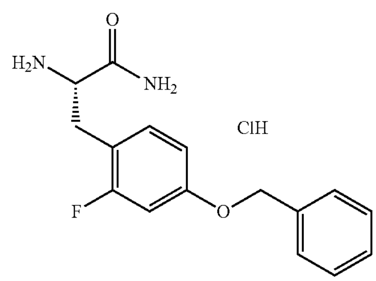


I-24.1

-continued



I-24.3



R47

Step 1: Synthesis of Intermediate I-24.1

R22 (22.58 g, 75.97 mmol) in Me-THF (50 mL) is cooled down to −10° C., 1,1,3,3-tetramethylguanidine (9.55 mL, 75.97 mmol) is added and stirred for 30 min. 4-benzyloxy-2-

fluoro-benzaldehyde (15.9 g, 69.06 mmol) dissolved in 100 mL Me-THF is added dropwise and stirred for 3 h at −10° C. to 0° C. The cooling is removed and the mixture warms up to room temperature.

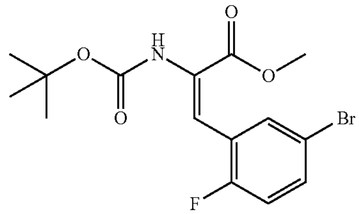
The reaction mixture is diluted with 300 mL Me-THF and extracted with water. The organic layer is treated with activated carbon, dried over $MgSO_4$ and concentrated.

The crude product is recrystallized with cyclohexane and filtered off.

Yield 97%, m/z 402 [M+H]+, rt 0.80 min, LC-MS Method X018_S01.

The following intermediate as shown in Table 50.1 is synthesized in an analogous manner from the appropriate intermediates:

TABLE 50.1

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-24.1.1		374/376	0.77	X018_S02

Step 2: Synthesis of Intermediate I-24.2

I-24.1 (2.8 g, 6.98 mmol) and (+)-1,2-bis((2s,5s)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium(I) trifluoromethanesulfonate (250 mg, 0.346 mmol) in methanol (60 mL) are stirred under hydrogen (50 psi) at r.t. for 2 h. Then the mixture is filtered and the filtrate is concentrated. Yield 100%, m/z 404 [M+H]+, rt 1.40 min, LC-MS Method V001_S01.

The following intermediates as shown in Table 51 are synthesized in an analogous manner from the appropriate intermediates:

TABLE 51

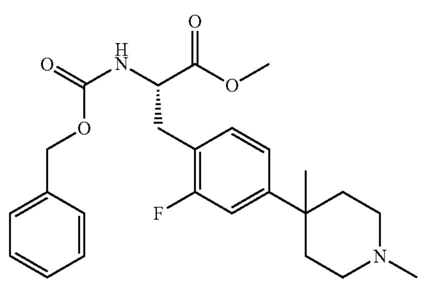
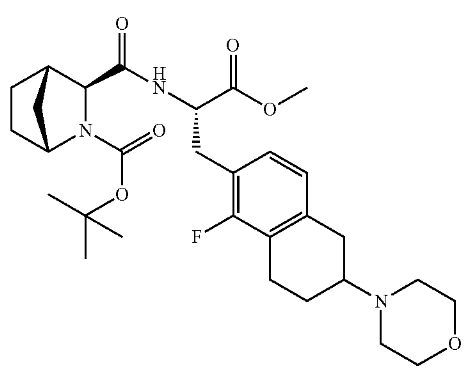
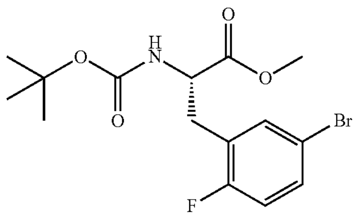
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-24.2.1		443	1.24	V011_S01
I-24.2.2		560	0.68	X011_S03

TABLE 51-continued

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-24.2.3		376	n.d.	n.d.

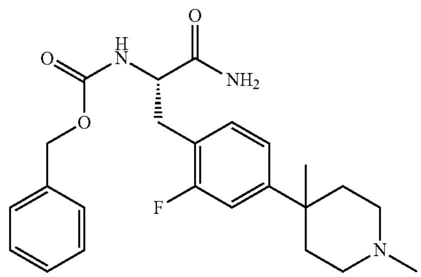
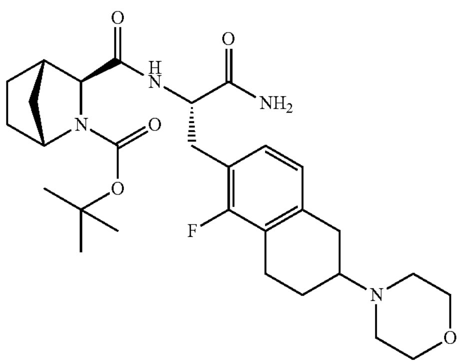
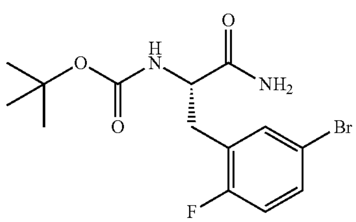
Step 3: Synthesis of Intermediate I-24.3

I-24.2 (2.95 g, 6.95 mmol) is dissolved in anhydrous methanol (15 mL). Calcium chloride (812 mg, 7.32 mmol) and ammonia in methanol 7N (15 mL, 10.5 mmol) is added and stirred at r.t. overnight. The reaction mixture is diluted with water (45 mL) and the precipitate is filtered off and washed with water.

Yield 90%, m/z 389 [M+H]+, rt 0.65 min, LC-MS Method X011_S03.

The following intermediate as shown in Table 52 is synthesized an analogous manner from the appropriate intermediates:

TABLE 52

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-24.3.1		428	1.05	V011_S01
I-24.3.2		545	0.57	X011_S03
I-24.3.3		361/363	0.64	X018_S02

Intermediate I-24.3.1 is purified by reversed phase HPLC.

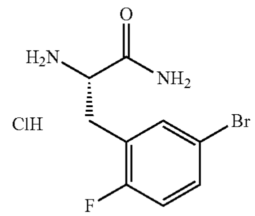
Step 4: Synthesis of R47

To I-24.3 (2.42 g, 6.23 mmol) in dichlormethane (20 mL) is added HCl in dioxane 4 mol/L (7.79 mL, 31.15 mmol) and stirred at r.t. for 3 h. The reaction mixture is diluted with TBME and the precipitate is filtered off and washed with TBME.

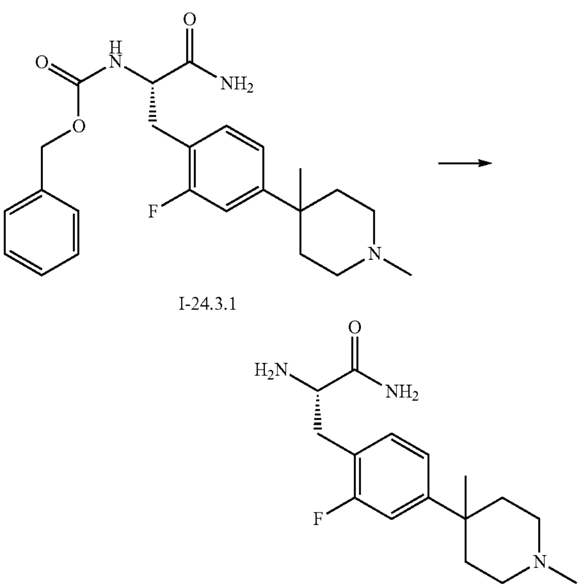
Yield 95%, m/z 289 [M+H]+, rt 0.50 min, LC-MS Method X011_S03.

The following intermediate as shown in Table 52.1 is synthesized in an analogous manner from the appropriate intermediates:

TABLE 52.1

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R47.1		261/263	0.31	X018_S02

Synthesis of (2S)-2-amino-3-[4-(1,4-dimethyl-4-piperidyl)-2-fluoro-phenyl]propanamide R49



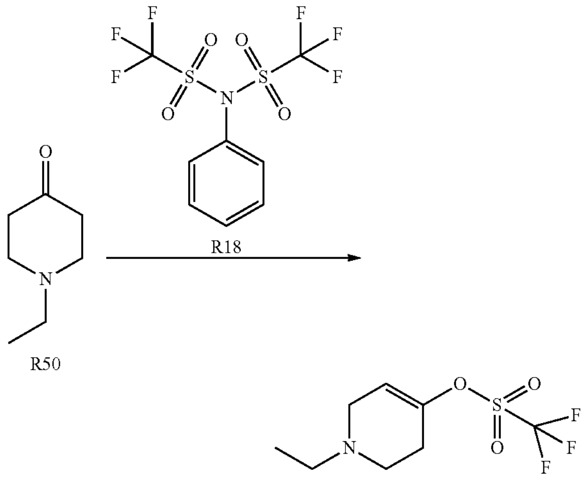
I-24.3.1

R49

I-24.3.1 (625 mg, 1.46 mmol) and Pd/C 10% (150 mg) in methanol (60 mL) is stirred under hydrogen (50 psi) at r.t. for 3.5 h. The reaction mixture is filtered and concentrated.

Yield 99%, m/z 294 [M+H]+, rt 0.80 min, LC-MS Method V011_S01.

Synthesis of (1-ethyl-3,6-dihydro-2H-pyridin-4-yl) trifluoromethanesulfonate (R51)



R50

R18

R51

The reaction is carried out under argon atmosphere.

Diisopropylamine (5.289 mL, 38 mmol) in anhydrous THF (25 mL) is cooled down to −50° C. N-butyllithium in hexane 2.5M (13.786 mL, 34.47 mmol) is added dropwise and stirred for 45 min, then the solution is allowed to warm up to 0° C. and cooled down to −50° C. again. 1-Ethyl-4-piperidone (4 g, 31.45 mmol) dissolved in 30 mL THF is added dropwise and stirred for 30 min. R18 (11.797 g, 33.02 mmol) dissolved in 30 mL THF is added dropwise. The cooling is removed and the reaction mixture stirred for 2 h.

The reaction mixture is diluted with 50 mL toluene. The organic layer is washed with 1N sodium hydroxide, halfsaturated brine, dried and concentrated. The residue is purified over silica gel. Yield 15%, m/z 260 [M+H]+, rt 0.30 min, LC-MS Method X012_S01.

The following intermediates as shown in Table 53 are synthesized in an analogous manner from the appropriate intermediates:

TABLE 53

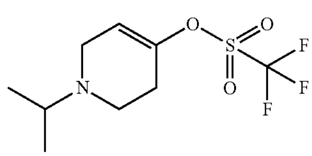
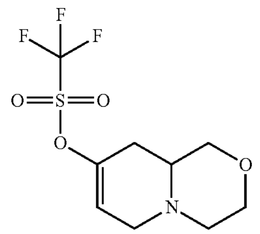
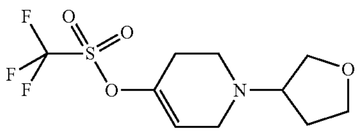
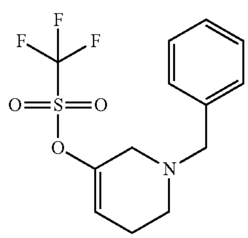
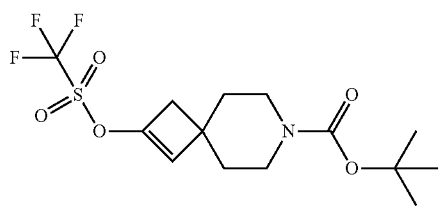
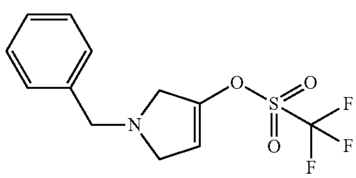
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R51.1		274	n.d.	n.d.

TABLE 53-continued

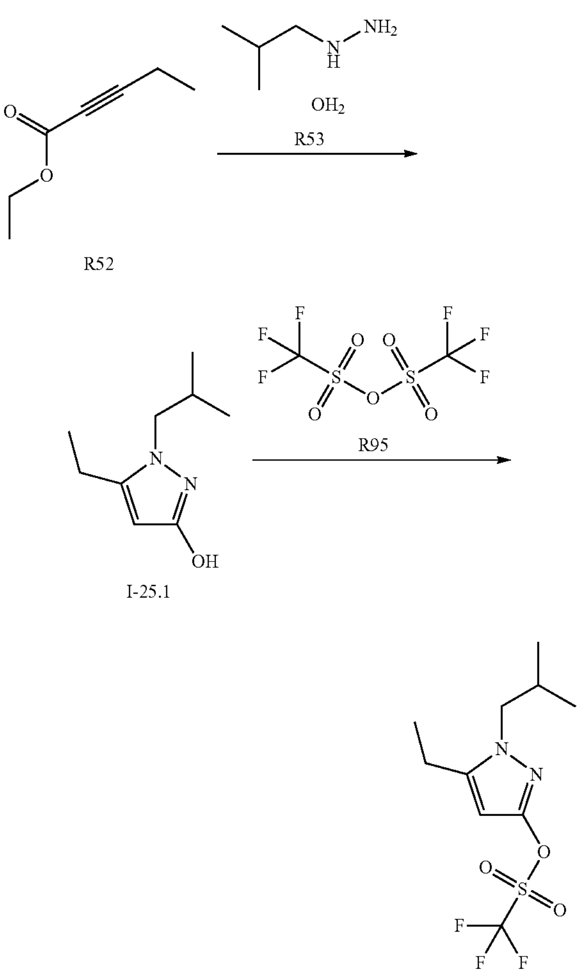
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R51.2		n.d.	n.d.	n.d.
R51.3		n.d.	n.d.	n.d.
R51.4		322	1.41	V011-S01
R51.5		316	1.23	Z012_S04
R51.6		308	1.38	V11_S01

For Intermediate R51.2, R51.3, R51.4 and R51.6 the reaction conditions differ: lithium bis(trimethylsilyl)amide is used and the reaction is carried out at −78° C. The crude product is used for the next step without further purification.

Intermediate R51.4 is purified over silica gel.

For Intermediate R51.5 the reaction conditions differ: lithium bis(trimethylsilyl)amide is used and the reaction is carried out at −50° C. The crude product is purified over silica gel.

Synthesis of (5-ethyl-1-isobutyl-pyrazol-3-yl)trifluoromethanesulfonate (R54)



R52 I-25.1 R54

Step 1: Synthesis of Intermediate I-25.1

Ethyl pent-2-ynoate (300 μL, 2 mmol), isobutylhydrazine hydrate (240 μL, 2 mmol), methanol (1 mL) and water (1 mL) are stirred together in the microwave at 140° C. for 15 min.

The crude product is used for the next step without further purification.

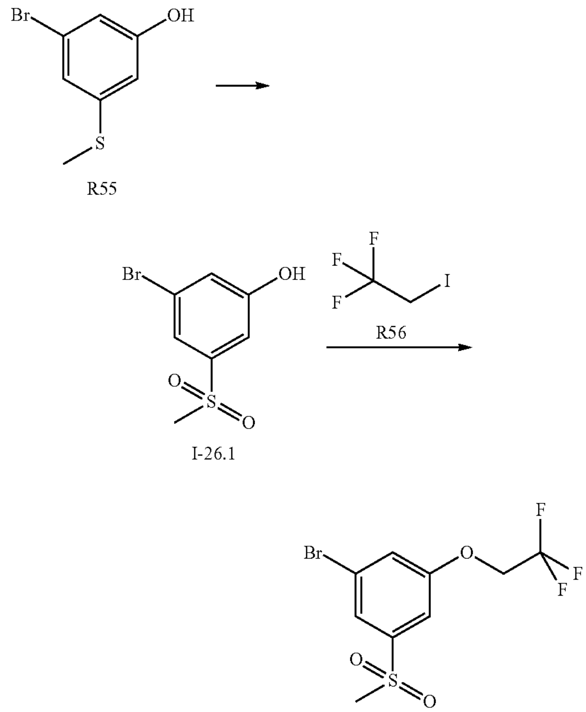
Step 2: Synthesis R54

Intermediate I-25.1 (380 mg, 2 mmol) is dissolved in anhydrous dichlormethane (10 mL), DIPEA (1.2 mL, 6.94 mmol) is added and cooled down to 0° C. Trifluoromethylsulfonyl trifluoromethanesulfonate

(375 μL, 2.26 mmol) dissolved in dichlormethane is added dropwise and stirred for 45 min. Another trifluoromethylsulfonyl trifluoromethanesulfonate (188 μL, 1.13 mmol) is added and stirred for 30 min. The reaction mixture is extracted with $NaHCO_3$-solution (5%). The organic layer is separated, dried and concentrated. The residue is purified over silica gel.

Yield 21%, m/z 301 [M+H]+, rt 0.86 min, LC-MS Method X018_S02.

Synthesis of 1-bromo-3-methylsulfonyl-5-(2,2,2-trifluoroethoxy)benzene (R57)



R55 I-26.1 R57

Step 1: Synthesis of Intermediate I-26.1

3-bromo-5-methylsulfanyl-phenol (5 g, 22.82 mmol) is dissolved in dichlormethane (100 mL) and cooled down to 0° C. 3-chloroperbenzoic acid (10.23 g, 45.64 mmol) is added and stirred at r.t. overnight. The reaction mixture is diluted with dichlormethane and water. The organic layer is separated, dried and concentrated. The crude product is purified by reversed phase HPLC and freeze dried.

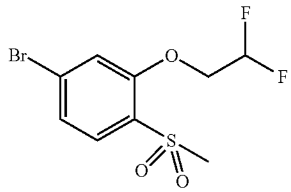
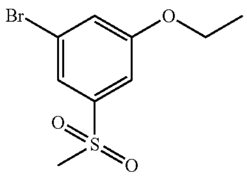
Yield 55%, m/z 251/253 [M+H]+, rt 0.47 min, LC-MS Method X018_S01.

Step 2: Synthesis R57

To I-26.1 (150 mg, 0.597 mmol) and potassium carbonate (206.41 mg, 1.49 mmol) in DMF is added 1,1,1-trifluoro-2-iodo-ethane (147.196 μL, 1.493 mmol) and stirred over 3 days at 85° C. The reaction mixture is diluted with water, the precipitate is filtered off, washed with water and dried. Yield 52%, m/z 350/352 [M+H]+, rt 1.16 min, LC-MS Method V011_S01.

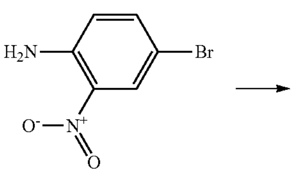
The following intermediates as shown in Table 54 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 54

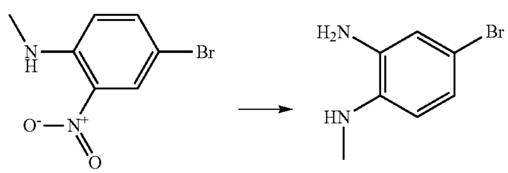
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method	elab
R57.1		332/334 [M + NH_4]+	1.01	V011_S01	LG1SLA00459
R57.2		296/298 [M + NH_4]+	1.11	V011_S01	LG1SLA00495

The two intermediates in the table above are purified by reversed phase HPLC.

Synthesis of 4-bromo-N1-methyl-benzene-1,2-diamine (R58)



R103



I-36.1 R58

Step 1: Synthesis of Intermediate I-36.1

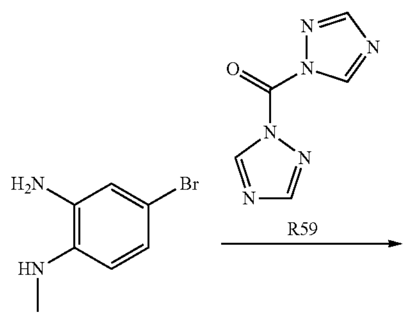
To 4-bromo-2-nitro-aniline (10 g, 46.08 mmol) in DMF (200 mL) are added potassium carbonate (15 g, 108.53 mmol) and portionwise methylamine hydrochloride (3.11 g, 46.08 mmol) and stirred overnight at r.t. The reaction mixture is filtered and concentrated. The crude product is triturated with DIPE, filtered off and dried. Yield 86%

Step 2: Synthesis of R58

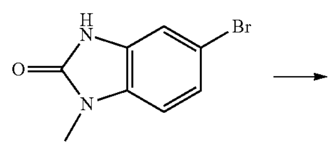
To I-36.1 (5.27 g, 22.81 mmol) in ethyl acetate is added platinum on carbon (550 mg) and stirred under hydrogen (5 bar) at r.t. for 4 h. The reaction mixture is filtered through a pad of celite and concentrated. The crude product is used without further purification for the next step

Yield 96%

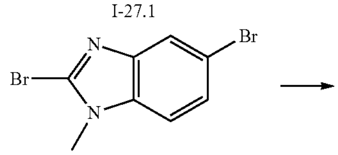
Synthesis of 5-bromo-N,1-dimethyl-benzimidazol-2-amine (R60)



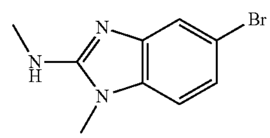
R58



I-27.1



I-27.2



R60

Step 1: Synthesis of Intermediate I-27.1

4-bromo-1-n-methylbenzene-1,2-diamine (4.42 g, 21.98 mmol), N,N'-carbonyl-di-(1,2,3-triazole (4.178 g, 24.18 mmol), and TEA (9.184 mL, 65.95 mmol) in THF (70 mL) are stirred at r.t. for 30 min, then heated under reflux overnight. The reaction mixture is concentrated, triturated with water, filtered off and dried. The residue is triturated again with DIPE and filtered off.

Yield 88%

Step 2: Synthesis of Intermediate I-27.2

I-27.1 (4.41 g, 19.42 mmol) and phosphoroxybromide (27.84 g, 97.11 mmol) are stirred at 100° C. for 3 h. The reaction mixture is diluted with iced water. The precipitate is filtered off and triturated with DIPE.

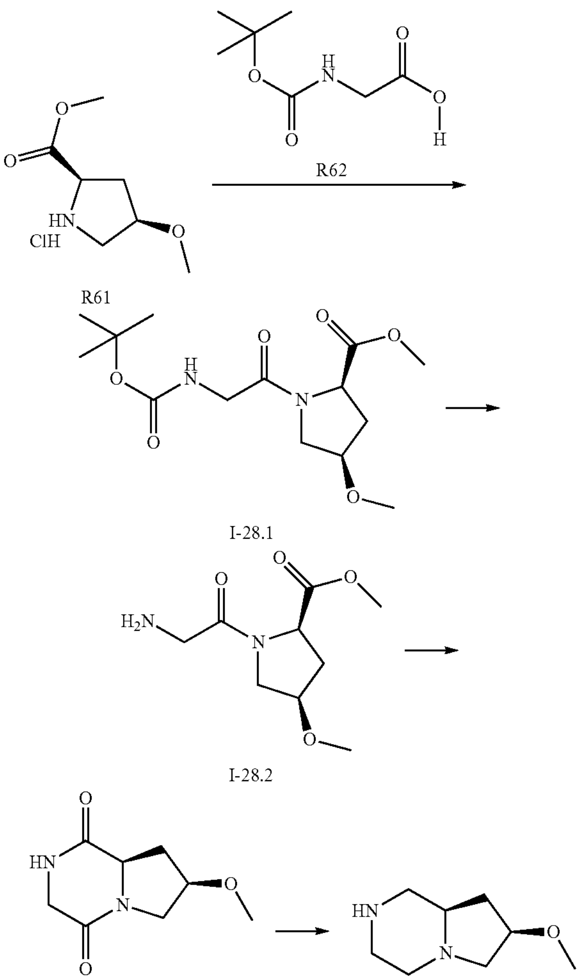
Yield 89%

Step 3: Synthesis of R60

I-27.2 (200 mg, 0.69 mmol) and methylamine in methanol 2 mol/L (2 mL, 4 mmol) are stirred at 80° C. for 16 h. The reaction mixture is purified by reversed phase HPLC.

Yield 63%, m/z 240/242 [M+H]+, rt 0.48 min, LC-MS Method X011_S03.

Synthesis of (7R,8aR)-7-methoxy-1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine (R63)



Step 1: Synthesis of Intermediate I-28.1

To 2-(tert-butoxycarbonylamino)acetic acid (1.5 g, 8.56 mmol) and HATU (3.58 g, 9.42 mmol) in DMF (15 mL) is added DIPEA (5.89 mL, 34.25 mmol) and stirred for 15 min. Methyl (2R,4R)-4-methoxypyrrolidine-2-carboxylate hydrochloride (1.675 g, 8.56 mmol) is added and stirred at r.t. overnight. The reaction mixture is diluted with dichlormethan and $NaHCO_3$-solution. The organic layer is separated and washed with brine, dried and concentrated. The crude residue is purified by reversed phase HPLC.

Yield 74%, m/z 317 [M+H]+, rt 0.47 min, LC-MS Method X018_S01.

Step 2: Synthesis of Intermediate I-28.2

I-28.1 (2 g, 6.32 mmol), hydrochloric acid in dioxane 4 mol/L (10 mL, 40 mmol) and dioxane (30 mL) are stirred at r.t. overnight. The reaction mixture is directly used for the next step.

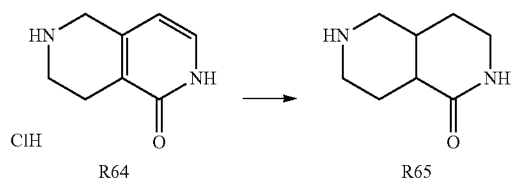
Step 3: Synthesis of Intermediate I-28.3

To the reaction mixture from the previous step is added TEA till a pH value of 8 is reached. The precipitate is filtered off and the mother liquor is concentrated to isolate the desired product. Yield 97%, m/z 185 [M+H]+, rt 0.18 min, LC-MS Method V011_S01.

Step 4: Synthesis of R63

To lithiumaluminium hydride 1 mol/L in THF (12.215 mL, 12.215 mmol) in THF (8 mL) is added a solution of I-28.3 (900 mg, 4.886 mmol) in THF (4 mL) dropwise and stirred at r.t. for 1.5 h. Under cooling the reaction mixture is poured into aq. sodium hydroxide (1 mol/L) and diluted with THF (30 ml). The precipitate is filtered off and the mother liquor is concentrated. The residue is diluted with methanol and stirred a few minutes at 50° C. The precipitate is filtered off and the mother liquor is concentrated to give the crude product which is purified over amino phase silica gel. Yield 36%

Synthesis of 3,4,4a,5,6,7,8,8a-octahydro-2H-2,6-naphthyridin-1-one (R65)

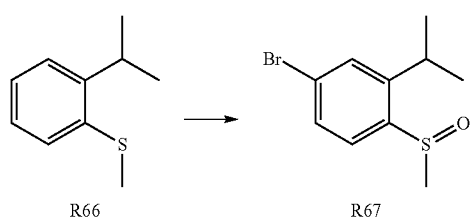


5,6,7,8-tetrahydro-2H-2,6-naphthyridin-1-one hydrochloride (250 mg, 1.339 mmol), platinum oxide (100 mg) and glacial acetic acid (10 mL) are stirred under hydrogen (5 bar) at r.t. for 24 h.

The reaction mixture is filtered off and concentrated. The crude product is purified over amino phase silica gel.

Yield 71%.

Synthesis of 4-bromo-2-isopropyl-1-methylsulfinyl-benzene (R67)

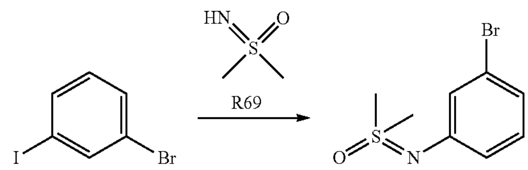


1-isopropyl-2-methylsulfanyl-benzene (400 mg, 2.41 mmol) is dissolved in dichlormethane (4 mL) and cooled down to 0° C. Bromine (123.21 µL, 2.41 mmol) is added and stirred at r.t. for 3 days.

The reaction mixture is concentrated and purified by reversed phase HPLC.

Yield 53%, m/z 261/263 [M+H]+, rt 1.06 min, LC-MS Method V011_S01.

Synthesis of (3-bromophenyl)imino-dimethyl-oxo-sulfane (R70)



R68 R69 R70

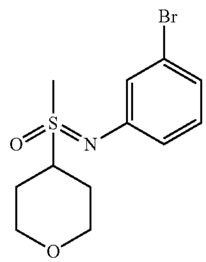
1-Bromo-3-iodo-benzene (250 μL, 1.96 mmol), (methylsulfonimidoyl)methane (219.188 mg, 2.353 mmol), cesium carbonate (894.466 mg, 2.745 mmol) and dioxane (12 mL) are purged with argon. (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (85.098, 0.147 mmol) and tris(dibenzylideneacetone)dipalladium(0) (44.89 mg, 0.049 mmol) are added, purged again with argon and stirred at 105° C. for 3 h.

The reaction mixture is filtered through a pad of celite. The filtrate is concentrated and purified by reversed phase HPLC.

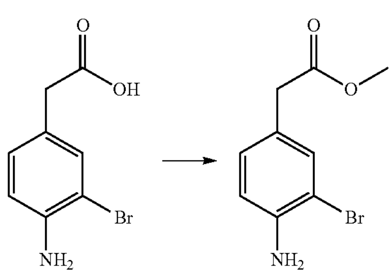
Yield 94%, m/z 249 [M+H]+, rt 0.74 min, LC-MS Method Z018_S04.

The following intermediate as shown in Table 55 is synthesized in a similar fashion from the appropriate intermediates:

TABLE 55

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method	elab
R70.1		318	0.83	Z018_S04	CCCYUJ00250

Synthesis of 2-(4-amino-3-bromo-phenyl)-N-methyl-acetamide (R71)

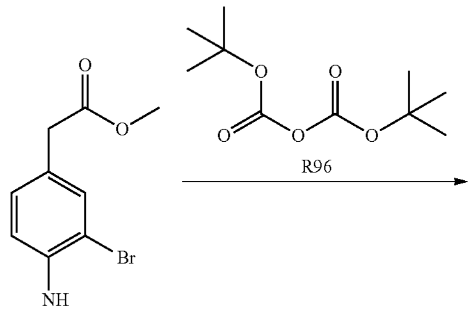


R102 R71

To 2-(4-amino-3-bromo-phenyl)acetic acid (5 g, 21.73 mmol) in methanol (50 mL) and dichlormethane (100 mL) is added at −5° C. trimethylsilyldiazomethane in diethylether 2 mol/L (31.51 mL, 63.03 mmol) dropwise over a period of 30 min. The reaction mixture is allowed to warm up to r.t. and concentrated. The crude product is used without further purification.

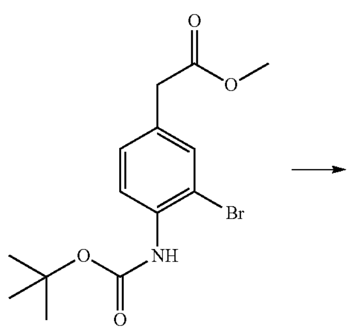
Yield 95%, m/z 244/246 [M+H]+, rt 0.48 min, LC-MS Method X011_S03.

Synthesis of 2-(4-amino-3-bromo-phenyl)-N-methyl-acetamide; 2,2,2-trifluoroacetic acid (R72)



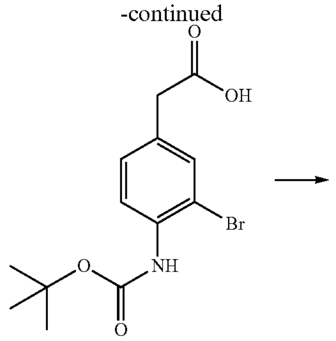
R71 R96

-continued

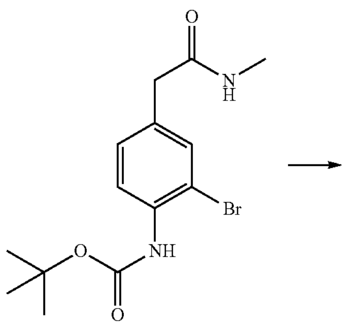


I-29.1

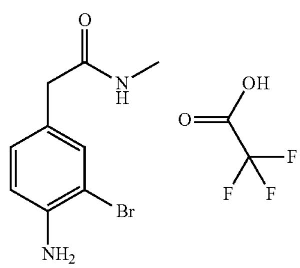
-continued



I-29.2



I-29.3



R72

Step 1: Synthesis of Intermediate I-29.1

4-amino-3-bromophenylacetic acid methyl ester (22 g, 81.12 mmol), di-t-butyl-dicarbonate (20.13 g, 92.22 mmol), 4-dimethylaminopyridine (991.02 mg, 8.11 mmol) and dichlormethane (300 mL) are stirred together at r.t. overnight. The reaction mixture is extracted with $KHSO_4$-solution (10%), $NaHCO_3$-solution and brine. The organic layer is separated, dried and concentrated. The residue is purified over silica gel.

Yield 8%, m/z 344/346 [M+H]+, rt 1.34 min, LC-MS Method V011_S01.

Step 2: Synthesis of Intermediate I-29.2

To I-29.1 (4 g, 11.62 mmol) in dioxane (50 mL) is added a solution of lithium hydroxide (400 mg, 13.95 mmol) in water (5 mL) and stirred at r.t. overnight. The precipitate is filtered by suction and dried.

Yield 91%, m/z 274/276 [M+H-isobutene]+, rt 0.29 min, LC-MS Method X011_S03.

Step 3: Synthesis of Intermediate I-29.3

To I-29.2 (150 mg, 0.45 mmol) in DMF (2 mL) is added TBTU (175.04 mg, 0.55 mmol) and after 7 min methylamine 2 mol/L in THF (0.9 ml, 1.82 mmol) is added. The reaction mixture is stirred at r.t. overnight and purified by reversed phase HPLC.

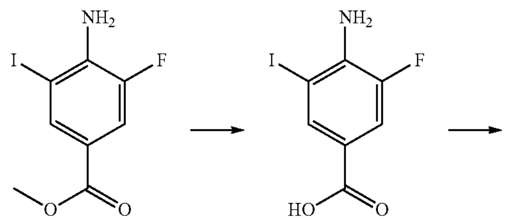
Yield 35%, m/z n.d. [M+H]+, rt 0.55 min, LC-MS Method X011_S03.

Step 4: Synthesis of R72

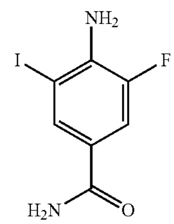
To I-29.3 (97 mg, 0.28 mmol) in dichlormethane (2 mL) is added trifluoracetic acid (0.5 mL) and stirred at r.t. for 1 h. The reaction mixture is concentrated.

Yield 99%, m/z 243/245 [M+H]+, rt 0.26 min, LC-MS Method X012_S01.

Synthesis of 4-amino-3-fluoro-5-iodo-benzamide (R74)



R73 I-30.1



R74

Step 1: Synthesis of Intermediate I-30.1

2-fluoro-6-iodo-4-(methoxycarbonyl)aniline (30 g, 0.1 mol), ethanol (300 mL) and NaOH 20% (30 mL) are stirred together under reflux for 2 h. The reaction mixture is diluted with water and acidified with $KHSO_4$-solution (1 mol/L). The precipitate is filtered off and recrystallized with ethanol.

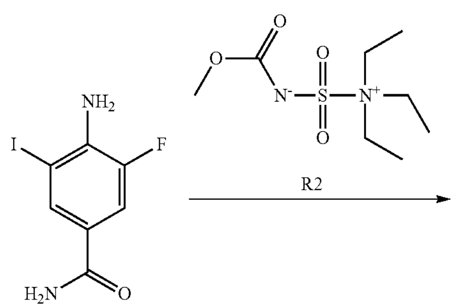
Yield 86%

Step 2: Synthesis of R74

To I-30.1 (26 g, 0.092 mol) in DMF (200 mL) is added 1,1'-carbonyldiimidazole (17.8 g, 0.11 mol) and ammonium carbonate (48 g, 0.5 mol) and stirred at 50° C. for 30 min. The reaction mixture is concentrated and the residue is diluted with water. The precipitate is filtered off and recrystallized with ethanol.

Yield 83%

Synthesis of 4-amino-3-fluoro-5-iodo-benzonitrile (R74.1)



R74

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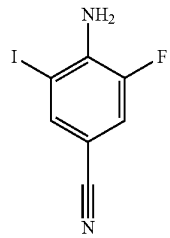
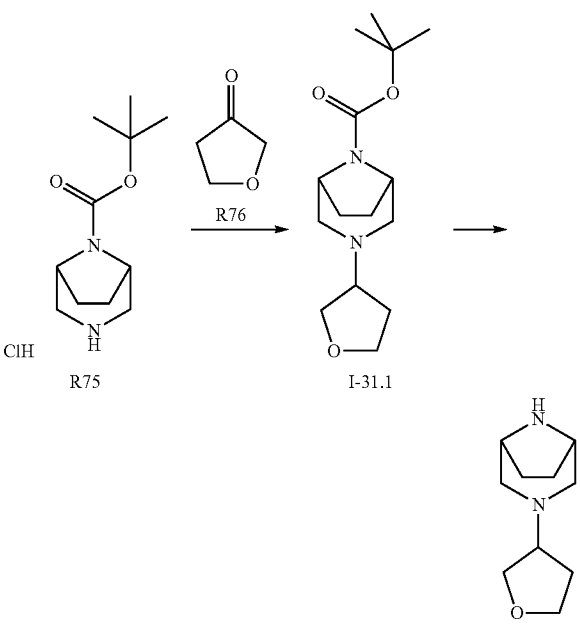


R74.1

To R74 (2 g, 7.14 mmol) in dichlormethane (50 mL) is added R2 (3.4 g, 14.28 mmol) and stirred at r.t. overnight. The reaction mixture is extracted with water. The organic layer is separated, dried and concentrated. The crude residue is filtered through a pad of silica gel (eluent (ethyl acetate/cyclohexane 3:7).

Yield 53%, m/z 263 [M+H]+, rt 0.47 min, LC-MS Method X012_S01.

Synthesis of 3-tetrahydrofuran-3-yl-3,8-diazabicyclo[3.2.1]octane (R77)



Step 1: Synthesis of Intermediate I-31.1

To tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate hydrochloride (300 mg, 1.21 mmol) in THF (5 mL) is added tetrahydrofuran-3-one (114.21 mg, 1.33 mmol) and sodium triacetoxyborhydride (349.78 mg, 1.57 mmol) and stirred at r.t. for 0.5 h.

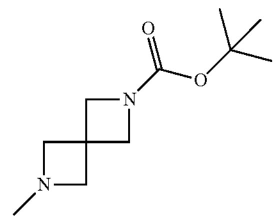
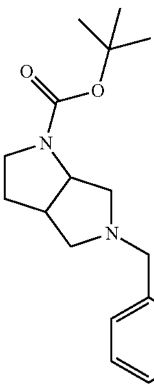
Sodium acetate (148.40 mg, 1.81 mmol) is added and stirred at r.t. overnight.

The reaction mixture is diluted with aq. sodiumhydrogen carbonate solution and extracted with ethyl acetate. The organic layer is separated, dried and concentrated. The crude residue is purified by reversed phase HPLC.

Yield 61%, m/z 283 [M+H]+, rt 0.61 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 56 are synthesized in an analogous manner from the appropriate intermediates:

TABLE 56

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-31.1.1		213	n.d.	n.d.
I-31.1.2		303	1.34	V11_S01

For I-31.1.1 sodium cyanoborhydride and methanol is used instead of sodium triacetoxyborhydride and THF.

Step 2: Synthesis of R77

I-31.1 (206 mg, 0.73 mmol) and hydrochloric acid in ether 1 mol/L (5 mL) is stirred at r.t. for 3 h. The reaction mixture is concentrated, diluted in dichlormethan/methanol 7/3 and filtered over amino phase silica gel.

Yield 99%, m/z 183 [M+H]+, rt 0.28 min, LC-MS Method V011_S01.

The following intermediates as shown in Table 56.1 are synthesized in an analogous manner from the appropriate intermediates:

TABLE 56.1

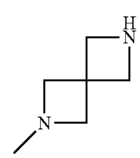
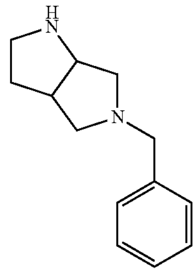
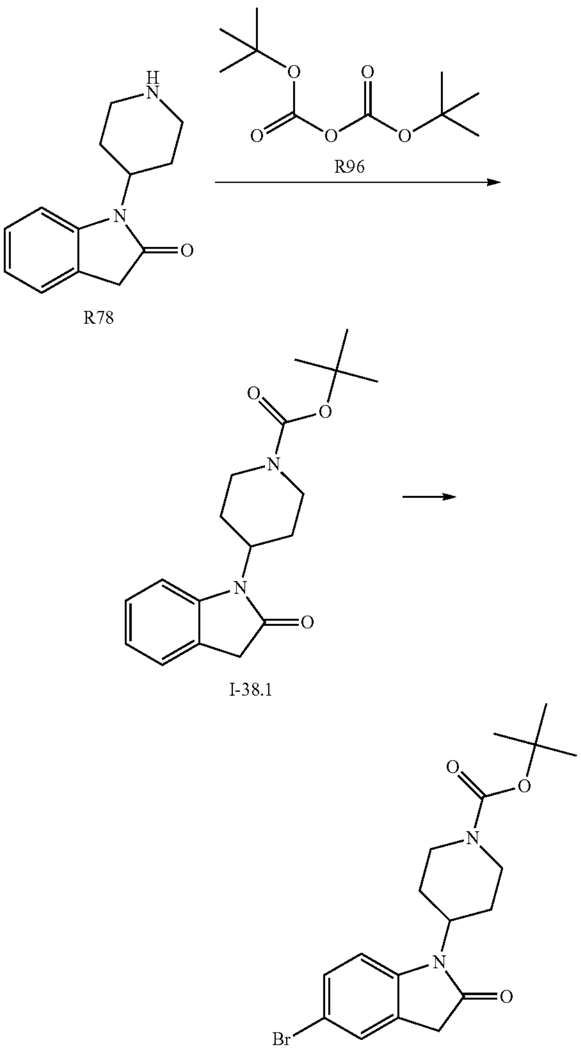
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R77.1		n.d.	n.d.	n.d.

TABLE 56.1-continued

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R77.2		203	0.91	V11_S01

For R77.1 p-toluenesulfonic acid monohydrate is used for the deprotection.

Synthesis of tert-butyl 4-(5-bromo-2-oxo-indolin-1-yl)piperidine-1-carboxylate (R79)



Step 1: Synthesis of Intermediate I-38.1

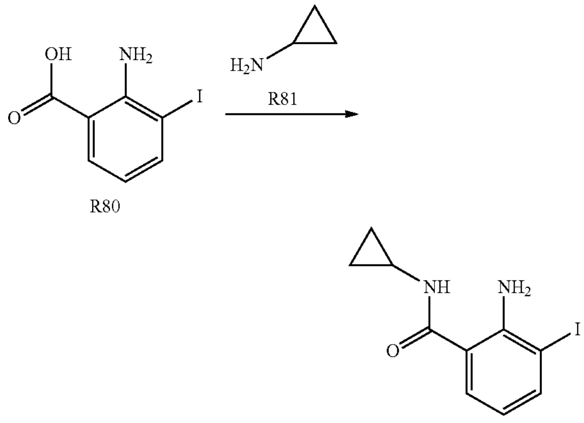
To 1,3-dihydro-1-(piperidin-4-yl)-(2H)-indol-2-one (200 mg, 0.93 mmol) in dichlormethane (5 mL) are added TEA (0.129 mL, 0.93 mmol) and di-t-butyl-dicarbonate (201.82

mg, 0.93 mmol). The reaction mixture is stirred for 10 min, diluted with water and sodium hydrogencarbonate solution and extracted with dichlormethane. The organic layer is dried and concentrated. Yield >95%, m/z 261 [M+H-tert.butyl]+, rt 1.055 min, LC-MS Method Z020_S01.

Step 2: Synthesis of R79

Tert-butyl 4-(2-oxoindolin-1-yl)piperidine-1-carboxylate (100 mg, 0.32 mmol) in ACN is cooled down to −10° C., N-bromosuccinimide (56.47 mg, 0.32 mmol) is added and stirred at −10° C. for 2 h. The reaction mixture is diluted with dichlormethane and water. The organic layer is separated, dried and concentrated. The crude product is used for the next step without further purification. Yield 99%, m/z 395 [M+H]+, rt 1.126 min, LC-MS Method Z020_S01.

Synthesis of 2-amino-N-cyclopropyl-3-iodo-benzamide (R82)

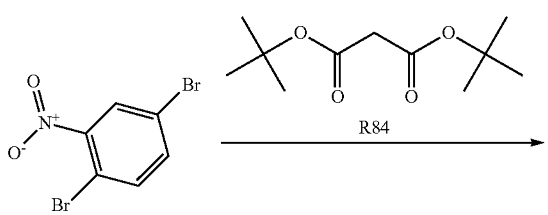


Synthesis of R82

To 2-amino-3-iodo-benzoic acid (200 mg, 0.76 mmol) in DMF (1 mL) TBTU (244.15 mg, 0.76 mmol) and DIPEA (245.69 µL, 1.52 mmol) are added and stirred at r.t. for 7 min. Cyclopropylamine (52.69 µL, 0.76 mmol) is added and stirred at r.t. overnight. The reaction mixture is diluted with water and the precipitate is filtered off and dried.

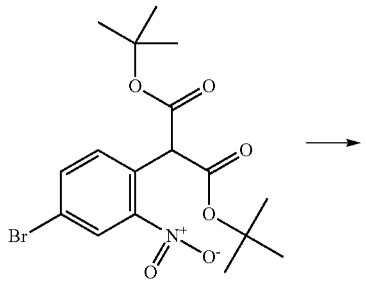
Yield 89%, m/z 303 [M+H]+, rt 0.49 min, LC-MS Method X012_S01.

Synthesis of 6-bromo-1-(1-methyl-4-piperidyl)indolin-2-one (R85)

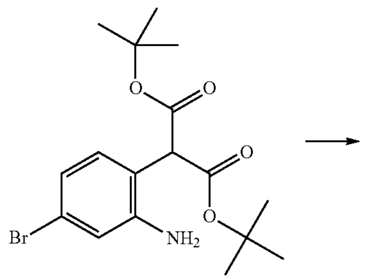


R83

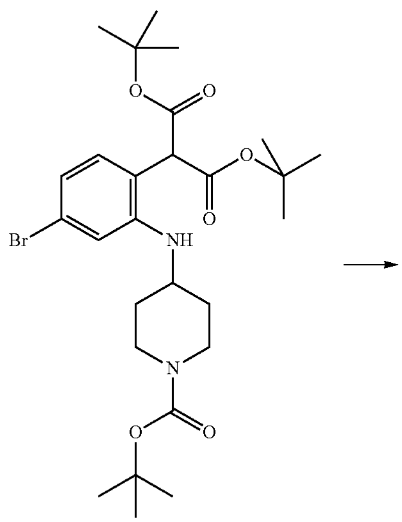
-continued



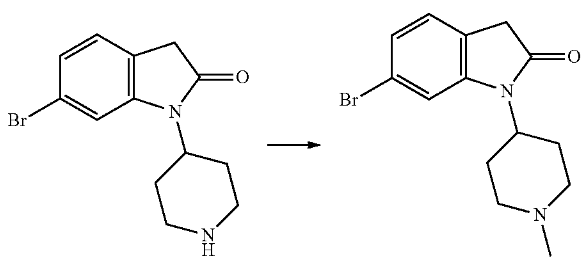
I-32.1



I-32.2



I-32.3



I-32.4 R85

Step 1: Synthesis of Intermediate I-32.1

To sodium hydride 60% (1.536 g, 38.4 mmol) in DMSO (30 mL) under nitrogen atmosphere is added di-tert.butylmalonate (8.61 mL, 38.4 mmol) dropwise. The reaction mixture is stirred at 100° C. for 1 h, cooled down to 10° C. and a solution of 2,5-dibromonitrobenzene (4.93 g, 17.55 mmol) in DMSO (25 mL) is added dropwise. After the addition the reaction mixture is stirred at 100° C. for 1 h again.

The reaction mixture is poured into ammoniumchloride solution and the pH is adjusted with sodium hydrogensulfate to pH 7. Water and a mixture of ethylycetate/cyclohexane 1/1 is added. The aq. layer is extracted with this mixture. The organic layer is separated, washed with brine, dried and concentrated. The crude product is used for the next step without further purification. Yield 45%, m/z 414/416 [M+H]+, rt 1.215 min, LC-MS Method Z011_S03.

Step 2: Synthesis of Intermediate I-32.2

To I-32.1 (1 g, 2.4 mmol) in ethanol is added platinum on carbon (50 mg) and stirred under hydrogen (50 psi) at r.t. for 67 h. The reaction mixture is filtered and concentrated. The crude residue is purified by reversed phase HPLC.

Yield 34%, m/z 274/276 [M+H]+, rt 1.156 min, LC-MS Method Z011_S03.

Step 3: Synthesis of Intermediate I-32.3

To I-32.2 (316.66 mg, 0.81 mmol) in dichlormethane (2 mL) and glacial acetic acid (73.88 mL, 1.22 mmol) are added Boc-4-piperidone (210.41 mg, 1.06 mmol), titanium (IV) isopropoxide (346.17 mg, 1.22 mmol) and sodium triacetoxyborhydride (258.14 mg, 1.22 mmol) and stirred at 50° C. for 3 h and at r.t. over 3 days. The reaction mixture is diluted with dichlormethane and water. The organic layer is separated and concentrated. The crude product is purified by reversed phase HPLC. Yield 27%, m/z 569/571 [M+H]+, rt 1.049 min, LC-MS Method Z011_U03.

Step 4: Synthesis of Intermediate I-32.4

To I-32.3 (125.3 mg, 0.2 mmol) in toluene (1 mL) is added 4-ethyl-benzenesulfonic acid (163.9 mg, 0.9 mmol) and stirred at 140° C. by microwave irradiation. The reaction mixture is concentrated and diluted with sodium hydroxide 1 mol/L and dichlormethane and concentrated again. The crude product is used without further purification for the next step.

Yield 92%, m/z 295/7 [M+H]+, rt 0.867 min, LC-MS Method Z011_S03.

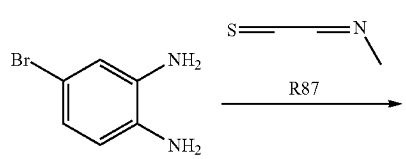
Step 5: Synthesis of R85

To I-32.4 (60 mg, 0.20 mmol) in methanol (1 mL) are added formaldehyde in water (37%) (75.67 μL, 1.02 mmol) and glacial acetic acid (17.44 μL, 0.31 mmol), stirred at r.t. for 75 min, afterwards sodium triacetoxyborhydride (107.70 mg, 0.51 mmol) is added. The reaction mixture is stirred at r.t. overnight.

The reaction mixture is diluted with sodium hydroxide 1 mol/L and dichlormethane. The organic layer is separated, washed with brine, dried and concentrated. The crude product is used for the next step without further purification.

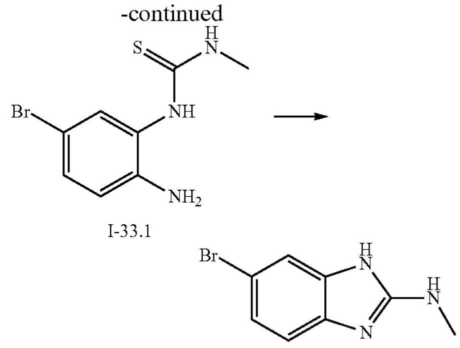
Yield 52%, m/z 309/311 [M+H]+, rt 0.912 min, LC-MS Method Z011_S03.

Synthesis of 6-bromo-N-methyl-1H-benzimidazol-2-amine (R88)



R86

-continued



I-33.1

R88

Step 1: Synthesis of Intermediate I-33.1

To 4-bromobenzene-1,2-diamine (0.5 g, 3 mmol) in dichlormethane (10 mL) and DIPEA (0.55 mL, 3 mmol) is added methylimino(thioxo)methane (0.2 g, 3 mmol) and stirred at 50° C. for 4 h and at r.t. overnight. The reaction mixture is extracted with, aq. acetic acid (1%), aq. sodium carbonate (10%) and brine. The organic layer is separated, dried and concentrated. The residue is purified over silica gel.

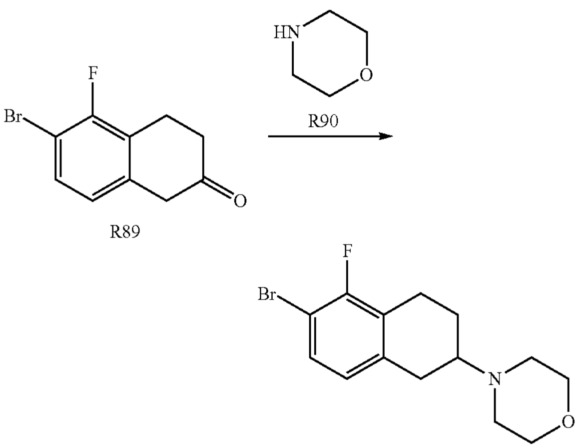
Yield 69%, m/z 260/262 [M+H]+, rt 0.45 min, LC-MS Method X018_S02.

Step 2: Synthesis of R88

To I-33.1 (130 mg, 0.50 mmol) in ACN (2.5 mL) are added benzotriazol-1-yl-oxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP reagent) (330 mg, 0.50 mmol) and DBU (150 μL, 1.00 mmol) and stirred at r.t. for 0.5 h. The reaction mixture is purified by reversed phase HPLC.

Yield 51%

Synthesis of 4-(6-bromo-5-fluoro-tetralin-2-yl)morpholine (R91)



R90

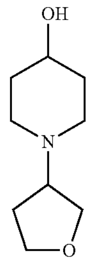
R89

R91

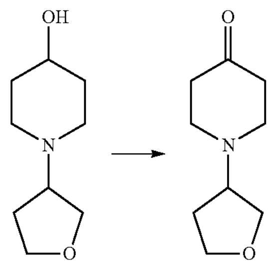
To 6-bromo-5-fluoro-tetralin-2-one (1 g, 4.11 mmol) and morpholine (0.36 mL, 4.11 mmol) in dichlormethane is added glacial acetic acid (0.52 mL, 9.05 mmol). The reaction mixture is cooled with an ice bath and sodium triacetoxyborhydride (1.74 g, 8.23 mmol) is added. The reaction mixture is stirred at r.t. overnight. Morpholine (0.2 mL) is added and stirred again at r.t. overnight. The reaction mixture is basified with potassium carbonate solution (20%) and stirred for 15 min. The organic layer is separated and the aq. layer is washed two times with dichlormethane. The organic layers are dried and concentrated. The crude product is purified by reversed phase HPLC Yield 57%, m/z 314/316 [M+H]+, rt 0.68 min, LC-MS Method X011_S03.

The following intermediate as shown in Table 57 is synthesized in a similar fashion from the appropriate intermediates:

TABLE 57

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R91.1		172	n.d.	n.d.

Synthesis of 1-tetrahydrofuran-3-ylpiperidin-4-one (R91.2)



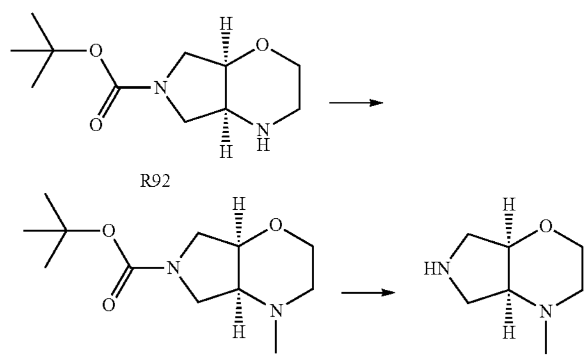
R91.1

R91.2

To R91.1 1-tetrahydrofuran-3-ylpiperidin-4-ol (200 mg, 1.17 mmol) in dichlormethane (5 mL) is added dess-martin periodine (595 mg, 1.40 mmol) and stirred at r.t. for 5 h. The reaction mixture is filtered through ALOX/N and washed with cyclohexane/ethyl acetate 1:3. The filtrate is concentrated.

Yield 51%

Synthesis of (4aS,7aR)-2,3,4,4a,5,6,7,7a-octahydropyrrolo[3,4-b][1,4]oxazine



R92

I-34.1

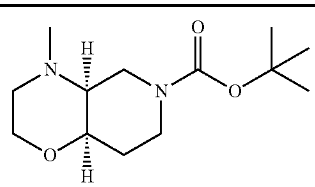
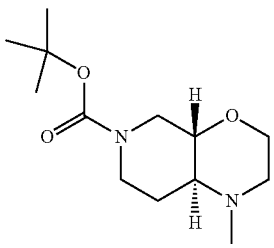
R93

Step 1: Synthesis of Intermediate I-34.1

To tert-butyl (4aS,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxylate (200 mg, 0.88 mmol) in methanol (3 mL) are added formaldehyde in water (37%) (26.44 mg, 0.33 mmol) and glacial acetic acid (79.71 mg, 1.31 mmol), stirred at r.t. for 75 min, afterwards sodium triacetoxyborhydride (464.19 mg, 2.19 mmol) is added. The reaction mixture is stirred at r.t. for 2 h Additional formaldehyde in water (37%) (26.44 mg, 0.33 mmol) is added and stirred in a 50° C. warm water bath for 10 min, sodium triacetoxyborhydride (464.19 mg, 2.19 mmol) is added and stirred at r.t. for 1.5 h. The reaction mixture is diluted with aq. sodium hydrogencarbonate solution and water and extracted with ethyl acetate. The organic layer is washed with aq. sodium hydrogencarbonate solution and brine, dried and concentrated. Yield 79

The following intermediates as shown in Table 58 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 58

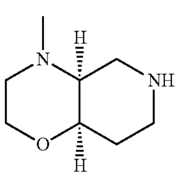
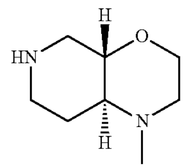
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
I-34.1.1		n.d.	n.d.	n.d.
I-34.1.2		n.d.	n.d.	n.d.

Step 2: Synthesis of R93

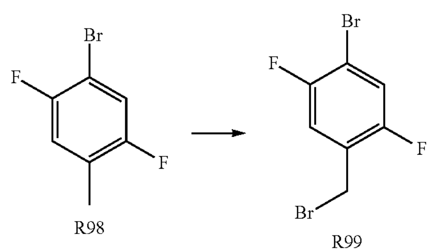
To I-34.1 (167 mg, 0.69 mmol) in dichlormethan (3 mL) p-toluenesulfonic acid monohydrate (655.48 mg, 3.45 mmol) is added and stirred at r.t. overnight. The reaction mixture is extracted with sodium hydroxide 1 mol/L. The organic layer is separated dried and concentrated. Due to less yield the aq. layer is saturated with sodium chloride and extracted with dichlormethane. The aq layer is concentrated and extracted again with dichlormethane. All organic layers are combine, dried and concentrated. Yield 76%

The following intermediates as shown in Table 59 are synthesized in a similar fashion from the appropriate intermediates:

TABLE 59

Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R93.1		n.d.	n.d.	n.d.
R93.2		n.d.	n.d.	n.d.

Synthesis of 1-bromo-4-(bromomethyl)-2,5-difluoro-benzene (R99)

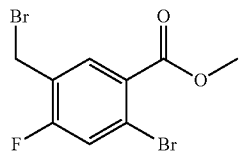


R98 (31.4 g, 15.17 mmol), N-bromosuccinimide (32.4 g, 1.6 mmol), AIBN (4.98 g, 30.34 mmol) in tetrachloromethane is heated at 90° C. overnight. The reaction mixture is cooled down to r.t. and concentrated. The residue is dissolved in ethyl acetate and extracted with water. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude product is purified by high vacuum distillation (boiling point 95° C.-98° C. by oil bath temperature of 140° C.)

Yield 67%

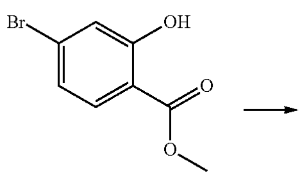
The following intermediate as shown in Table 60 is synthesized in an analogous manner from the appropriate intermediates:

TABLE 60

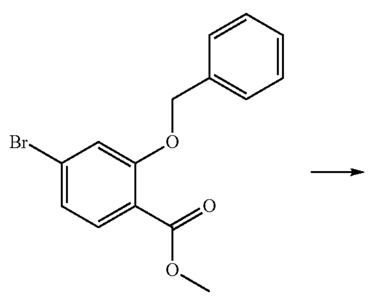
Intermediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R99.1		n.d.	0.65	X012_S01

For R99.1 the reaction temperature is 80° C. For the work up the reaction mixture is cooled to r.t. and the precipitate filtered off. The mother liquor is extracted with aq. hydrochloric acid (1 mol/L) and aq. sodium hydroxide (1 mol/L), dried and concentrated. The crude product is used without further purification.

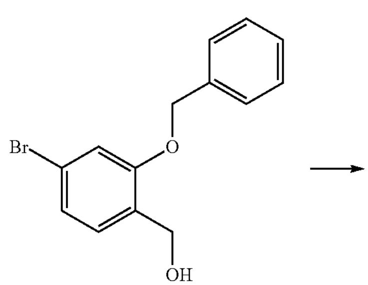
Synthesis of 2-benzyloxy-4-bromo-1-(chloromethyl)benzene (R100)



R101

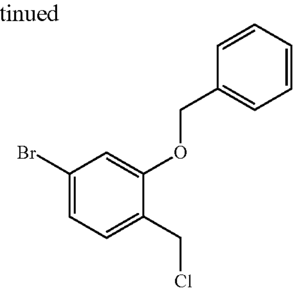


I-35.1



I-35.2

-continued



R100

Step 1: Synthesis of Intermediate I-35.1

To methyl 4-bromo-2-hydroxy-benzoate (4.3 g, 18.61 mmol) in acetonitrile (50 mL) are added bromomethylbenzene (2.23 mL, 19.54 mmol) and potassium carbonate (3.86 g, 27.92 mmol) and stirred for 4 h at reflux. The reaction mixture is cooled down to r.t., diluted with water and extracted with ethyl acetate. The organic layer is separated, dried over $MgSO_4$ and concentrated. The crude residue is purified over silica gel (eluent: cyclohexane/ethyl acetate 95:5). Yield 75%

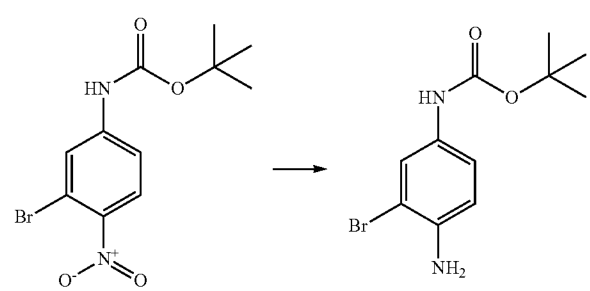
Step 2: Synthesis of Intermediate I-35.2

I-35.1 (4.5 g, 14.01 mmol) is dissolved in THF (50 mL) and a solution of lithium aluminium hydride in THF (8.41 mL, 8.41 mmol) is added dropwise between 5° C.-10° C. The reaction mixture is stirred 1 h under cooling and 1.5 h at r.t. Afterwards the mixture is cooled down and hydrolysed with 30 mL aq. hydrochloric acid (1 mol/L), diluted with water and extracted with ethyl acetate. The organic layer is washed with water, dried over $MgSO_4$ and concentrated. The crude residue is used for the next step without further purification. Yield 94%

Step 3: Synthesis of R100

To I-35.2 (3.85 g, 13.13 mmol) in dichlormethane (40 mL) is added triethylamine (2.21 mL, 15.76 mmol) and cooled down to 0° C.-2° C. Methanesulfonyl chloride (1.12 mL, 14.45 mmol) dissolved in dichlormethane (3 mL) is added dropwise. The reaction mixture is stirred for 1 h at 2° C.-5° C. and overnight at r.t. The reaction mixture is concentrated, diluted with dichlormethane and water. The organic layer is washed with 1 mol/L hydrochloric acid, water, dried over $MgSO_4$ and concentrated. The crude residue is used for the next step without further purification. Yield 74%

Synthesis of tert-butyl N-(4-amino-3-bromo-phenyl)carbamate (R104)

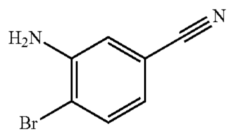


R105 R104

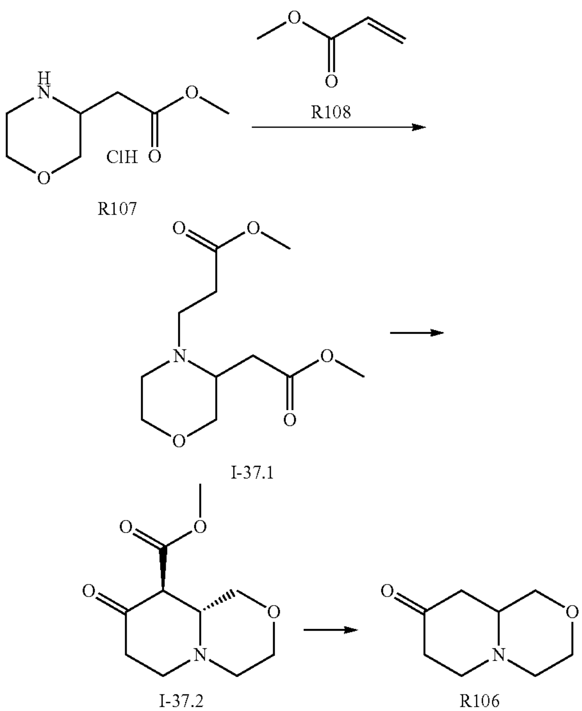
To tert-butyl N-(3-bromo-4-nitro-phenyl)carbamate (1 g, 3.15 mmol) in ethyl acetate (20 mL) is added tin (II) chloride dihydrate (3.56 g, 15.77 mmol) and stirred overnight at r.t. The reaction mixture is basified with potassium carbonate/sodium hydroxide. The organic layer is separated, dried and concentrated. The crude product is used without further purification for the next step. Yield 83%, m/z 287/289[M+H]+, rt 0.58 min, LC-MS Method X011_S03.

The following intermediate as shown in Table 61 is synthesized in an analogous manner from the appropriate intermediates:

TABLE 61

Inter-mediate	Structure	m/z [M + H]+	rt (min)	LC-MS method
R104.1		197/199	0.45	X012_S01

Synthesis of 3,4,6,7,9,9a-hexahydro-1H-pyrido[2,1-c][1,4]oxazin-8-one (R106)



Step 1: Synthesis of Intermediate I-37.1

To methyl 2-morpholin-3-ylacetate hydrochloride (1 g, 5.11 mmol) in methanol (25 mL) are added TEA (0.785 mL, 5.63 mmol) and acrylic acid methyl ester (0.465 mL, 5.16 mmol) and stirred overnight at r.t. Again acrylic acid methyl ester (0.465 mL, 5.16 mmol) is added and stirred 3 days at r.t. The reaction mixture is concentrated and the crude product is purified over silica gel (eluent: ethyl acetate).

Yield 93%, m/z 246[M+H]+, rt 0.77 min, LC-MS Method V011_S01.

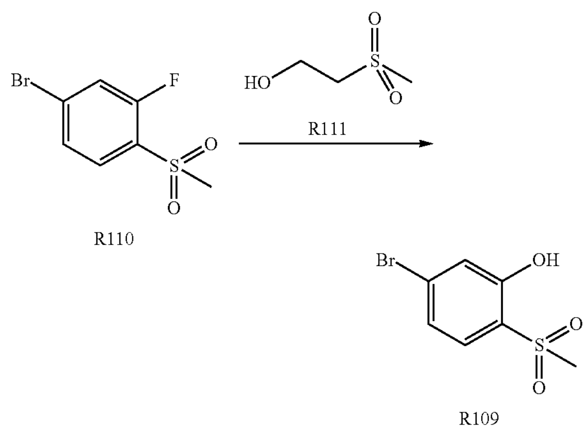
Step 2: Synthesis of Intermediate I-37.2

Under argon atmosphere I-37.1 (1.09 g, 4.44 mmol) is dissolved in THF (40 mL) and cooled down to −70° C. Lithium bis(trimethylsilyl)amide 1 mol/L (9 mL, 9 mmol) is added dropwise and stirred for 4 h at −70° C. The reaction mixture is quenched with hydrochloric acid 1 mol/L (15 mL). Afterwards solid sodium carbonate (1 g) is added. The aq. layer is extracted with ethyl acetate. The organic layers are combined, dried and concentrated. The crude product is purified over silica gel (eluent: ethyl acetate). Yield 68%

Step 3: Synthesis of R106

I-37.2 (0.63 g, 2.96 mmol) and hydrochloric acid 4 mol/L (15 mL) are stirred at 100° C. overnight. The reaction mixture is diluted with water and freeze-dried. The crude product is filtered over amino phase silica gel (eluent: dichlormethane/methanol). Yield 82%

Synthesis of 5-bromo-2-methylsulfonyl-phenol (R109)



To 4-bromo-2-fluoro-1-methylsulfonyl-benzene (2 g, 7.9 mmol) in DMF (15 mL) is added 2-methanesulfonyl-ethanol (1.47 g, 11.85 mmol). Sodium hydride (948.16 mg, 23.71 mmol) is added in portions at 0° C. The reaction mixture is allowed to come to r.t. and is added dropwise into cooled aq. hydrochloric acid. The aq. layer is extracted with ethyl acetate. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude residue is purified by reversed phase HPLC. Yield 86%, m/z 251/253[M+H]+, rt 0.42 min, LC-MS Method X018_S01.

Examples

(rt=retention time) Deprotection Methods: TSA (toluene sulfonic acid cf. Example 1), SI (trimethylsilyl iodide cf. example 2 or 3), FA (formic acid cf. example 4 or 7), TFA (trifluoroacetic acid). Stereochemistry at the carbon atom adjacent to the nitrile group is assigned: Stereo bond means S-isomer, non-stereo bond means 1:1 mixture of stereoisomers.

TABLE 62

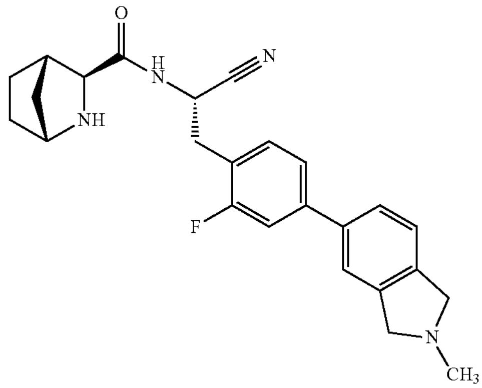
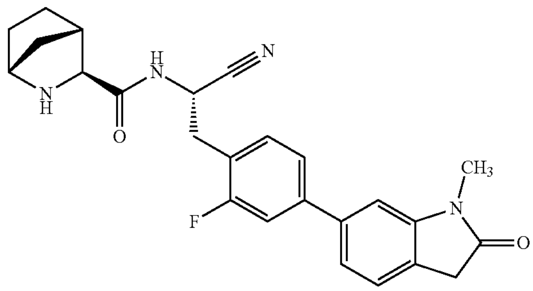
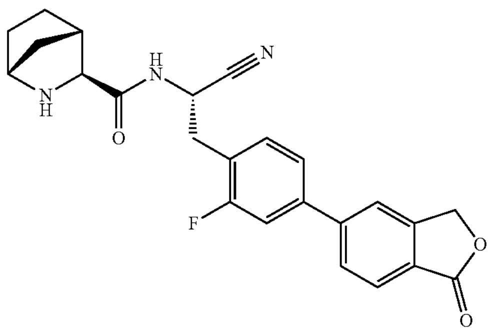
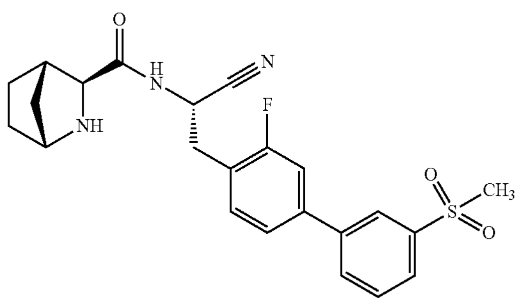
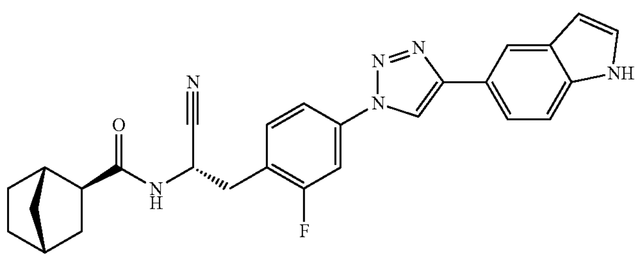
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
1		I-1.5	A/TSA	47
2		I-2.3	A1/SI	44
3		I-3.3	A2.1/SI	62
4		I-4.3	A3/FA	86
5		I-5.2	A4/FA	34

TABLE 62-continued

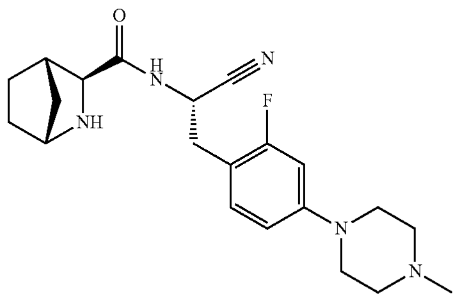
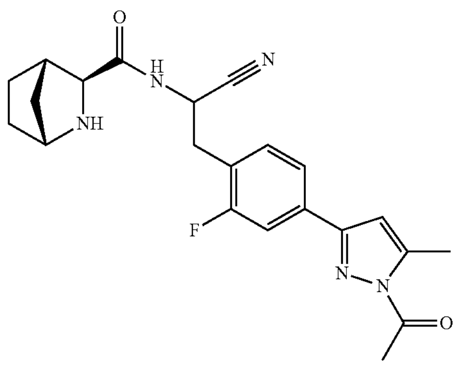
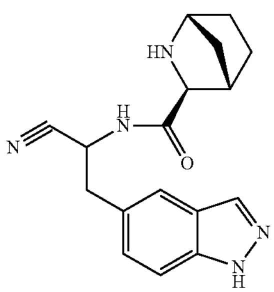
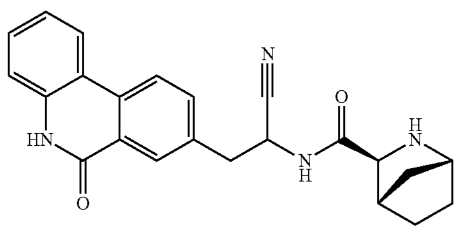
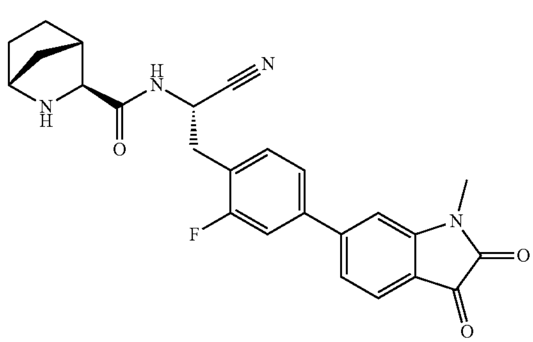
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
6		I-6.2	A5/TSA	86
7		I-7.3	B/FA	39
8		I-8.2	C/SI	19
9		I-9.1	D/SI	32
10		I-3.3.1	A2.1/SI	25

TABLE 62-continued

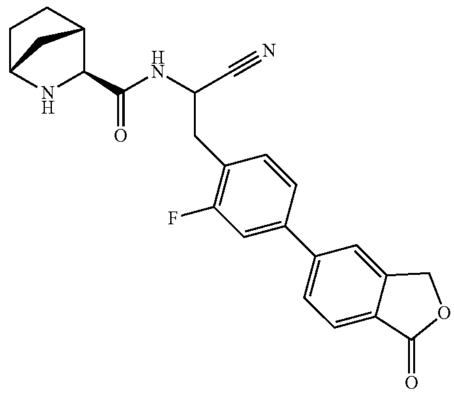
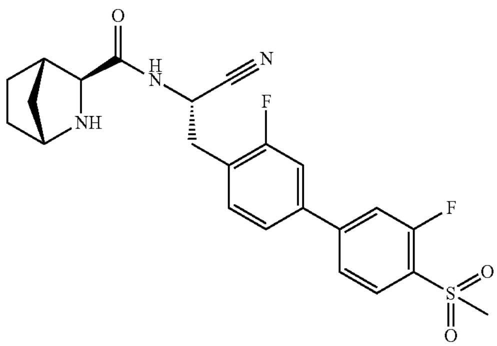
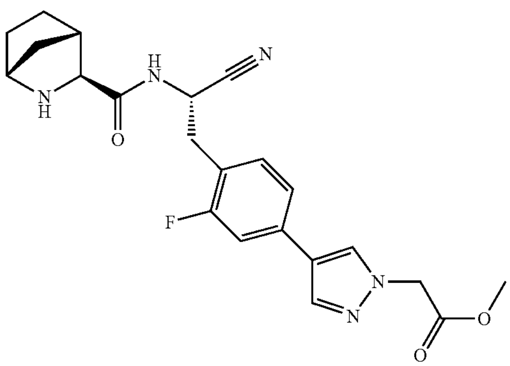
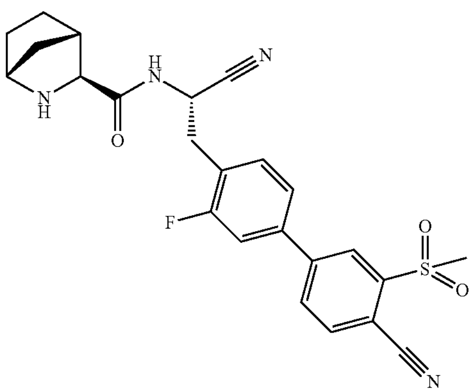
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
11		I-3.2.2	A2.1/SI	17
12		I-2.3.1	A1/FA	36
13		I-2.3.7.1	A1/FA	56
14		I-4.3.1	A3/SI	43

TABLE 62-continued

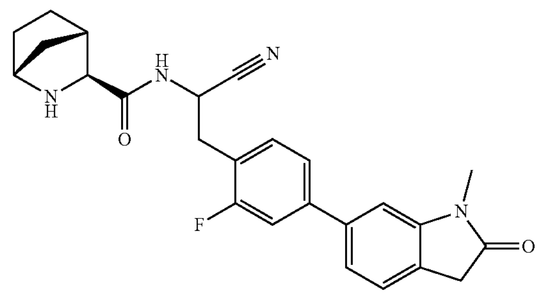
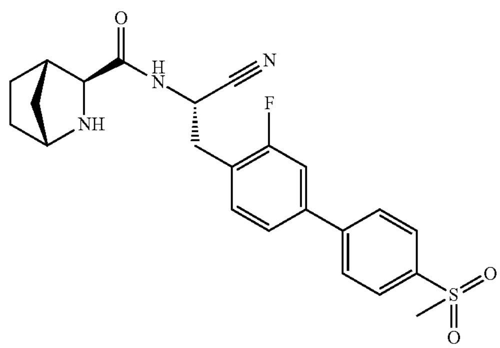
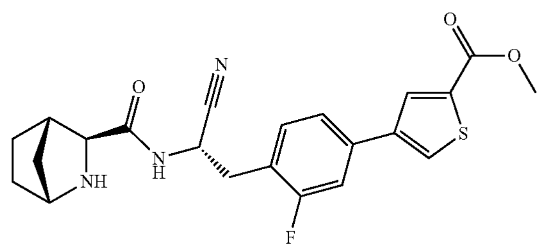
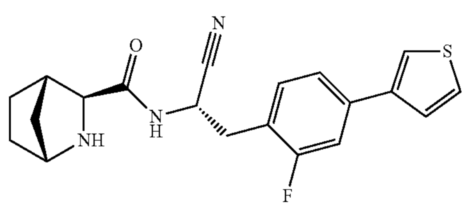
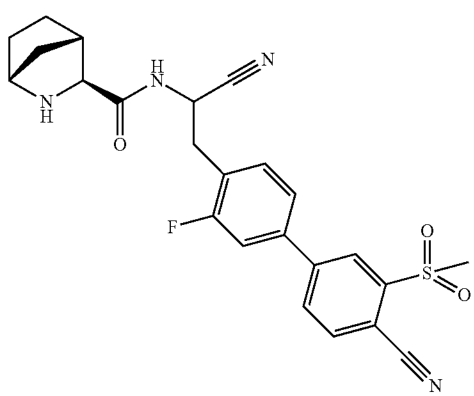
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
15		I-4.3.2	A3/SI	21
16		I-4.3.3	A3/TSA	93
17		I-2.3.2	A1/TSA	16
18		I-2.3.3	A1/TSA	36
19		I-4.3.1	A3/SI	59

TABLE 62-continued

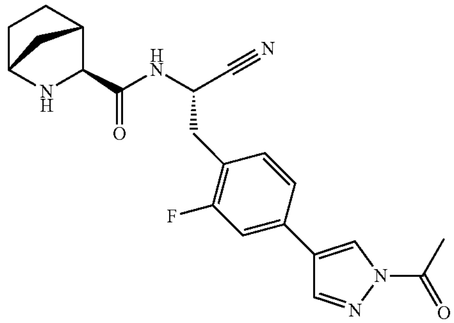
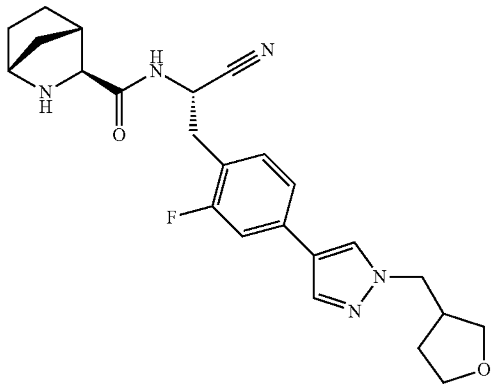
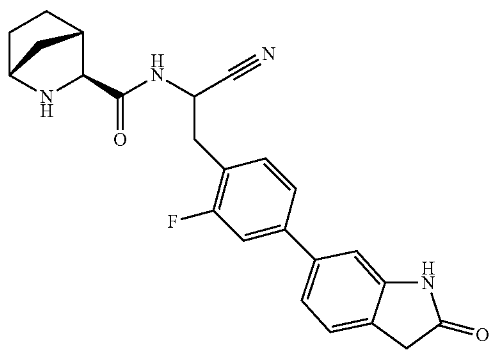
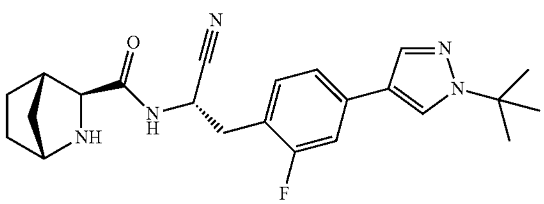
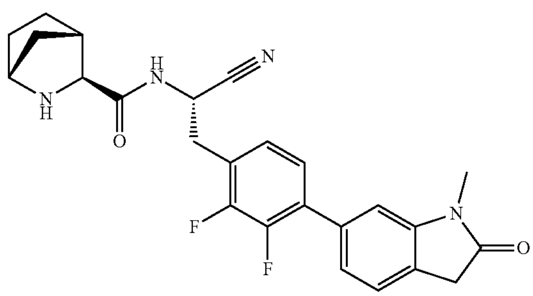
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
20		I-2.3.7.3	A1/TSA	22
21		I-2.3.7.4	A1/FA	49
22		I-4.3.5	A3/SI	70
23		I-2.3.4	A1/TSA	37
24		I-2.3.74.1	A1/TFA	45

TABLE 62-continued

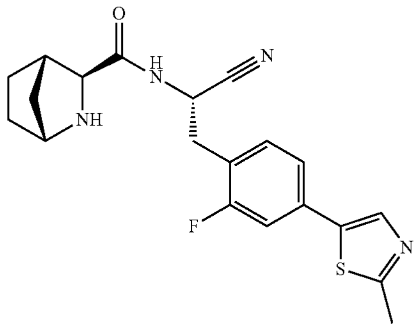
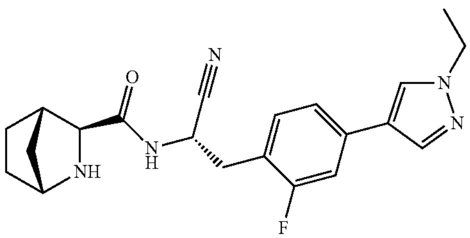
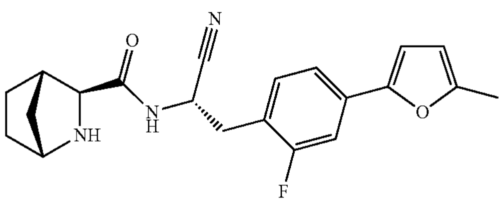
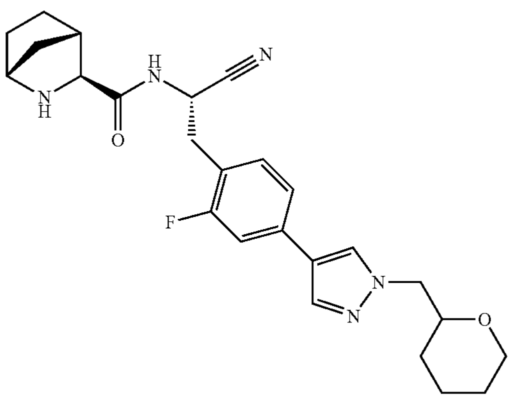
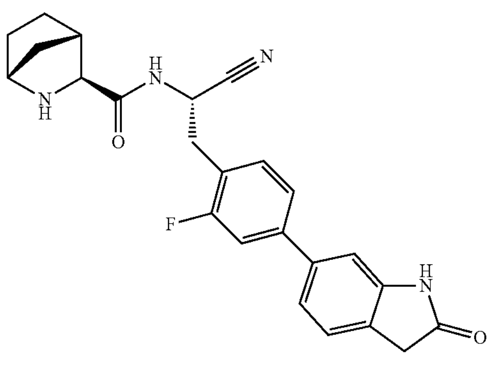
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
25		I-4.3.6	A3/TSA	45
26		I-2.3.5	A1/TSA	49
27		I-2.3.6	A1/TSA	38
28		I-2.3.7.5	A1/FA	75
29		I-4.3.7	A3/SI	40

TABLE 62-continued

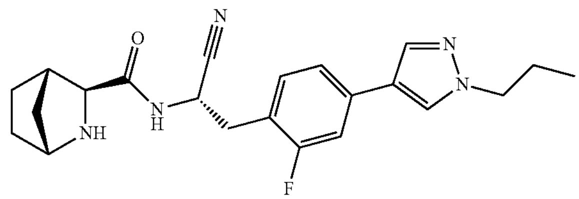
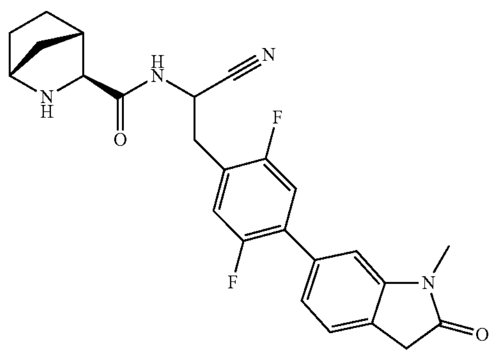
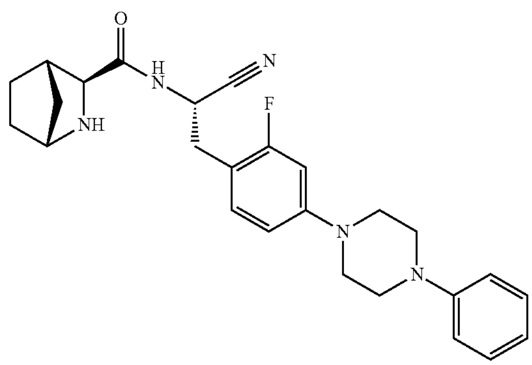
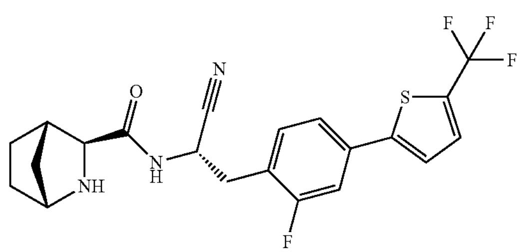
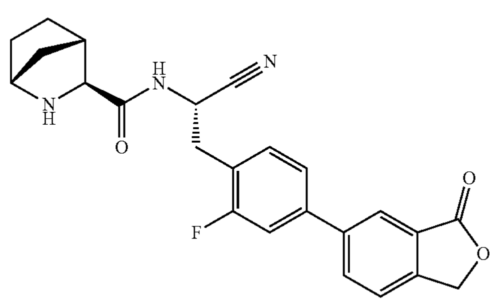
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
30		I-2.3.8	A1/TSA	46
31		I-4.3.8	A3/SI	39
32		I-3.2.4	A2.2/TSA	31
33		I-2.3.9	A1/TSA	16
34		I-3.3.3	A2.1/SI	32

TABLE 62-continued

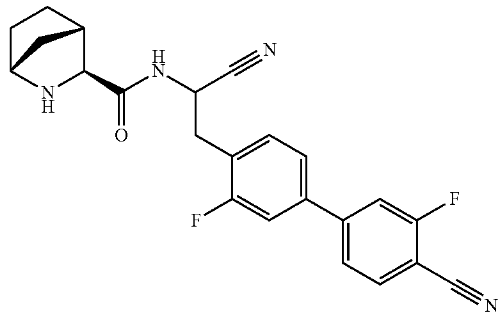
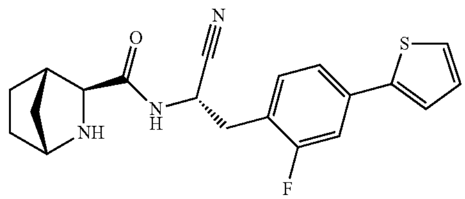
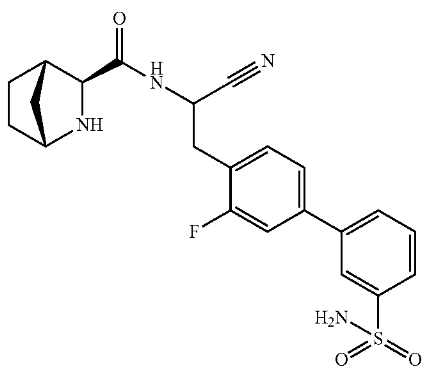
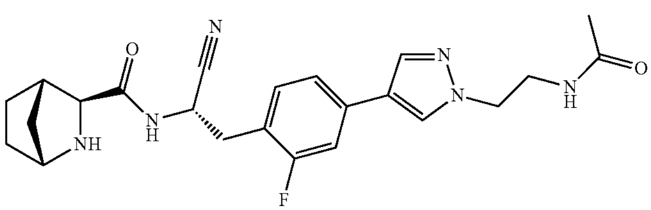
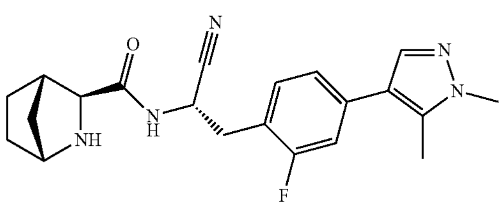
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
35		I-4.3.9	A3/SI	77
36		I-2.3.10	A1/TSA	39
37		I-4.3.10	A3/FA	98
38		I-2.3.11	A1/TSA	6
39		I-2.3.12	A1/TSA	30

TABLE 62-continued

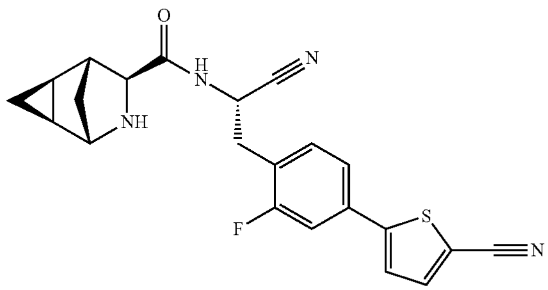
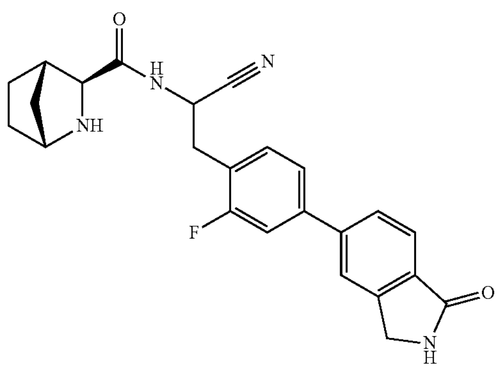
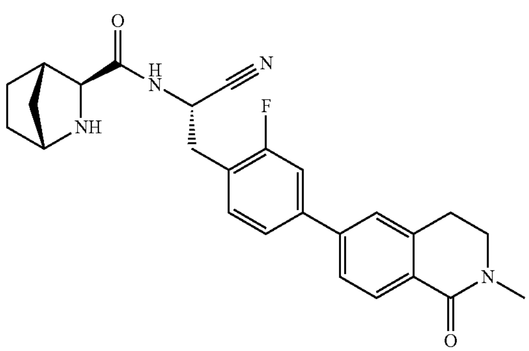
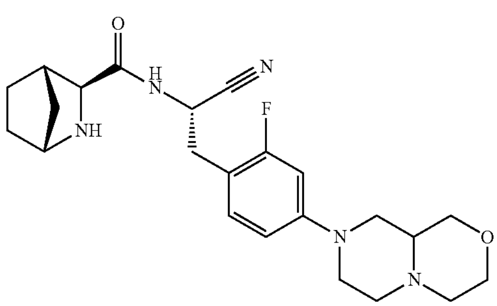
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
40		I-2.3.13	A1/TSA	49
41		I-4.3.11	A3/FA	>95
42		I-3.2.6	A2.1/TSA	75
43		I-3.2.7	A2.2/TSA	84

TABLE 62-continued

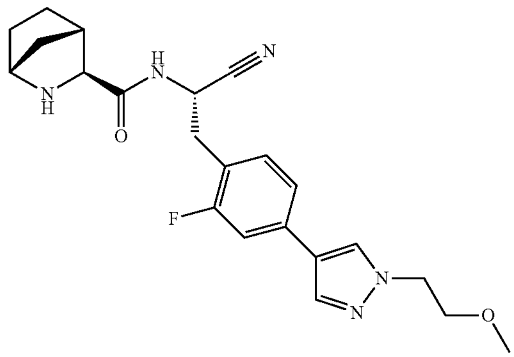
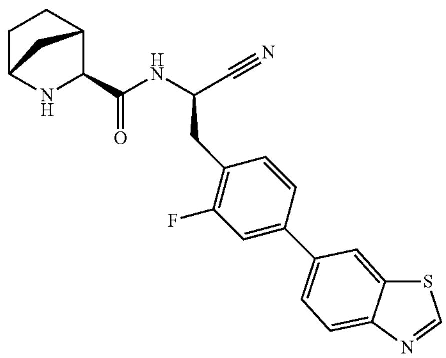
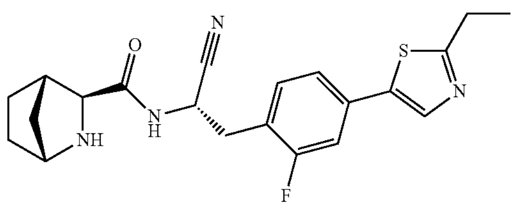
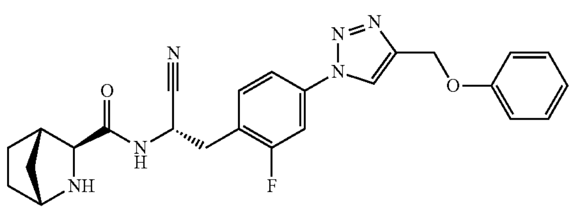
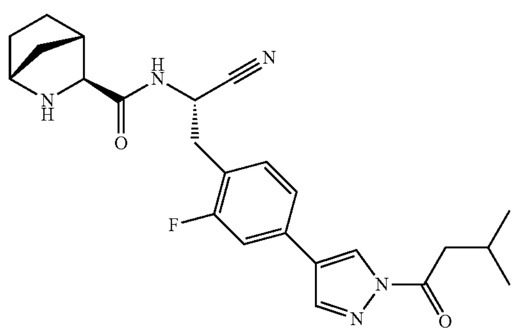
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
44		I-2.3.7.6	A1/FA	64
45		I-4.3.12	A3/SI	58
46		I-2.3.14	A1/TSA	12
47		I-5.2	A4/TSA	57
48		I-2.3.7.7	A1/FA	20

TABLE 62-continued

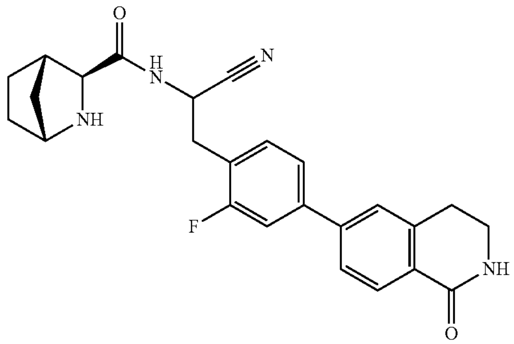
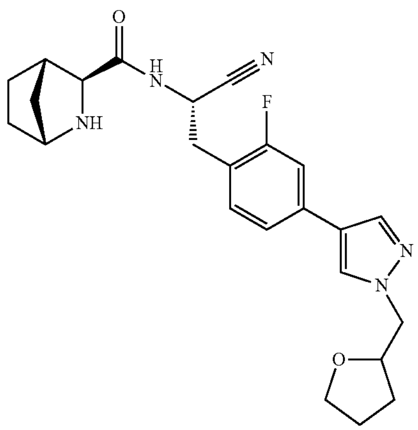
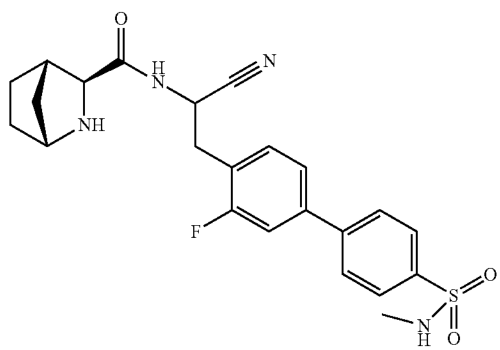
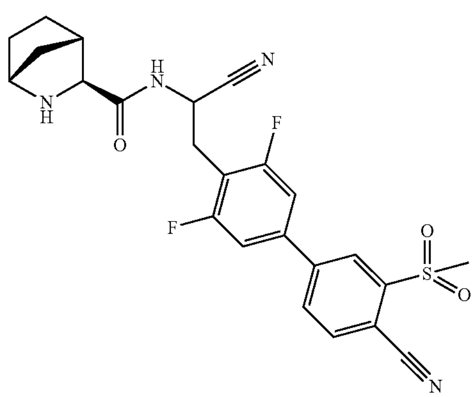
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
49		I-4.3.13	A3/FA	93
50		I-2.3.15	A1/TFA	31
51		I-4.3.14	A3/FA	76
52		I-4.3.4	A3/SI	33

TABLE 62-continued

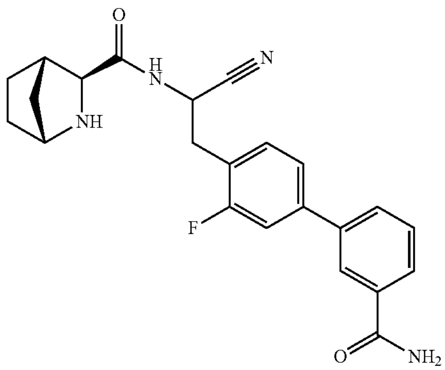
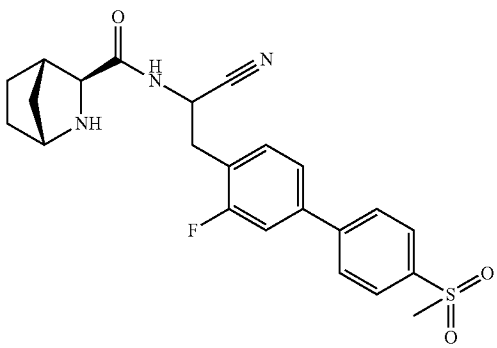
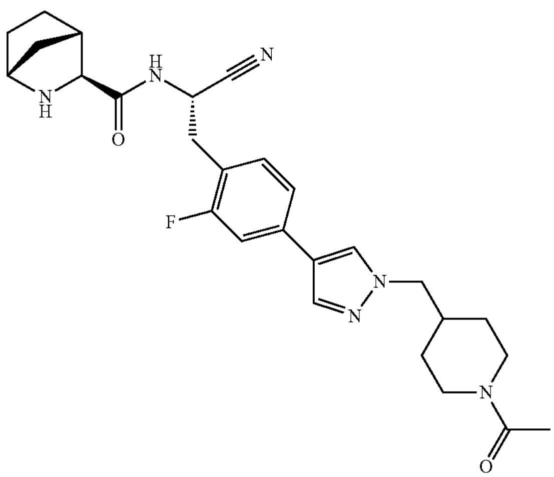
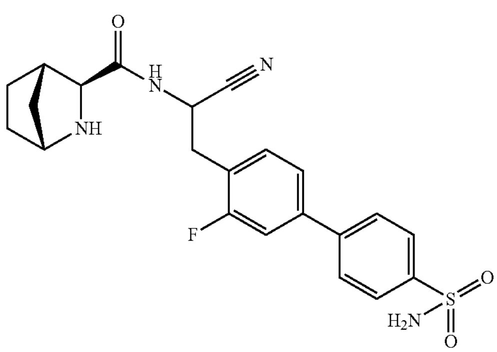
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
53		I-4.3.16	A3/FA	85
54		I-4.3.17	A3/FA	96
55		I-2.3.7.8	A1/FA	71
56		I-4.3.18	A3/FA	67

TABLE 62-continued

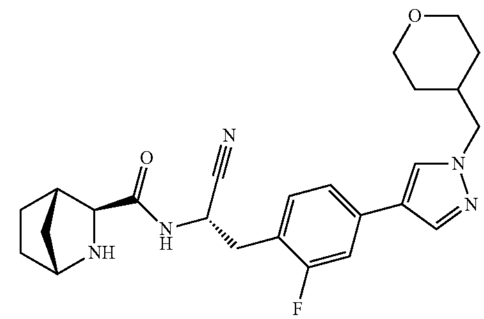
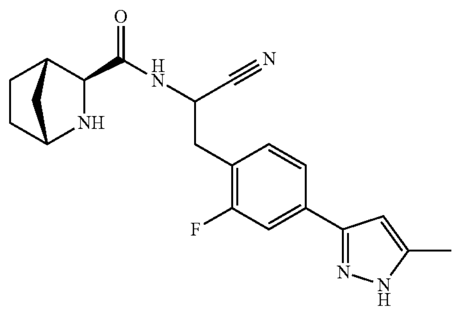
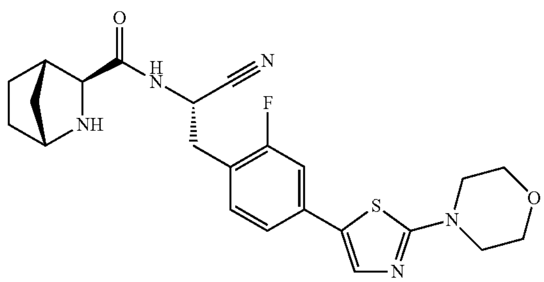
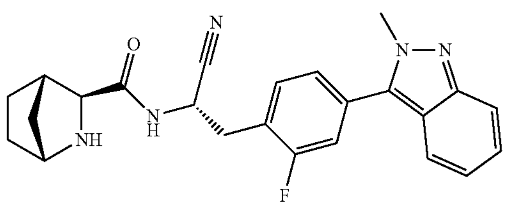
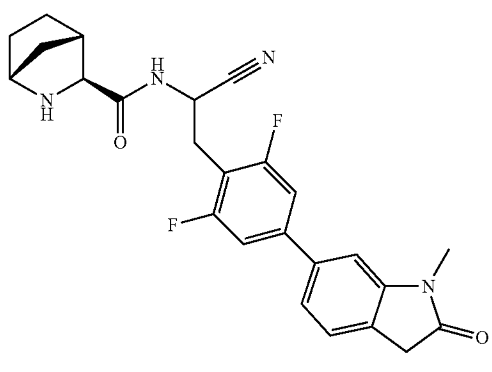
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
57		I-2.3.16	A1/TSA	38
58		I-7.3	B/FA	90
59		I-2.3.17	A1/FA	37
60		I-2.3.18	A1/TSA	33
61		I-4.3.15	A3/SI	47

TABLE 62-continued

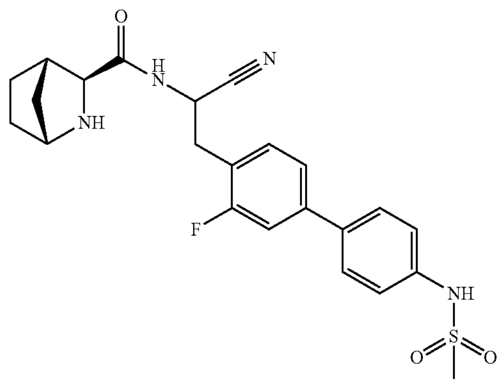
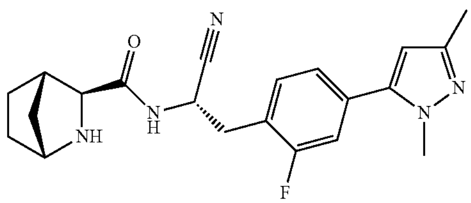
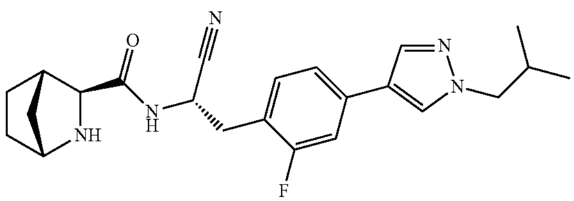
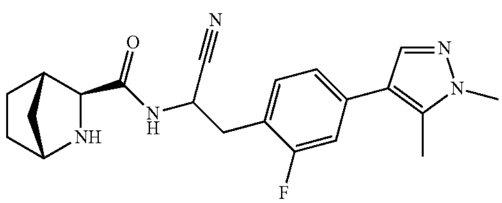
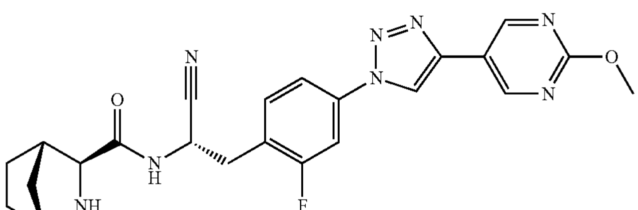
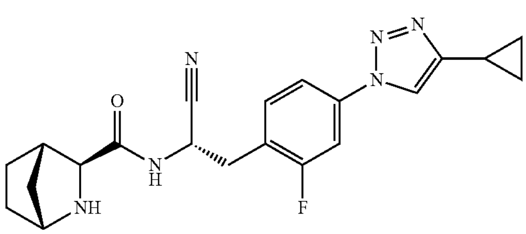
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
62		I-4.3.20	A3/FA	91
63		I-2.3.19	A1/TSA	19
64		I-2.3.20	A1/TSA	48
65		I-2.3.21	A1/TSA	6
66		I-5.2	A4/TSA	23
67		I-5.2	A4/TSA	53

TABLE 62-continued

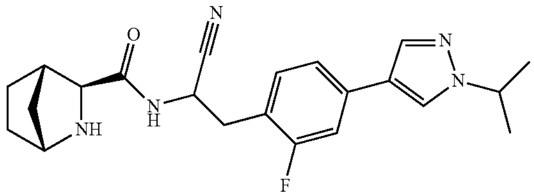
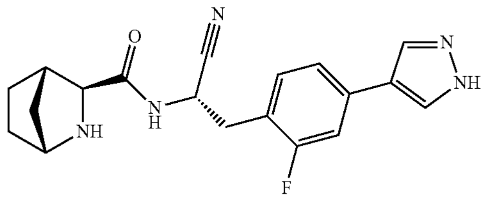
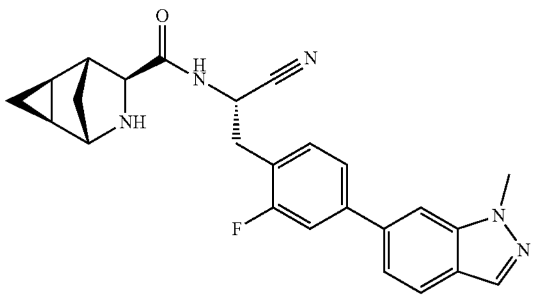
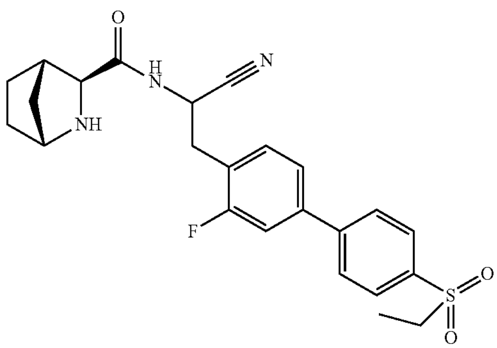
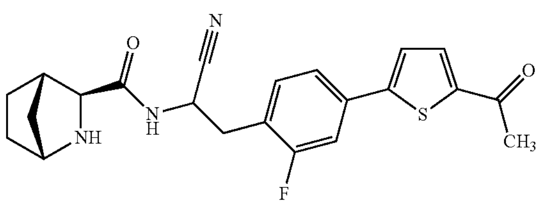
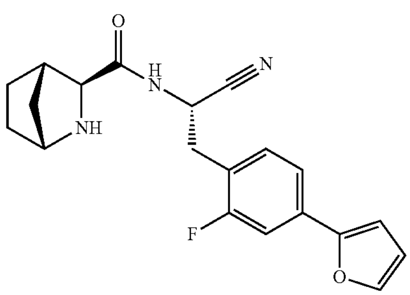
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
68		I-2.3.22	A1/TSA	17
69		I-2.3.23	A1/TSA	19
70		I-2.3.24	A1/TSA	58
71		I-4.3.21	A3/FA	>95
72		I-2.3.25	A1/TSA	13
73		I-2.3.26	A1/TSA	53

TABLE 62-continued

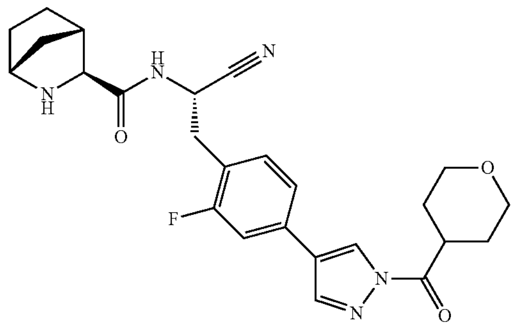
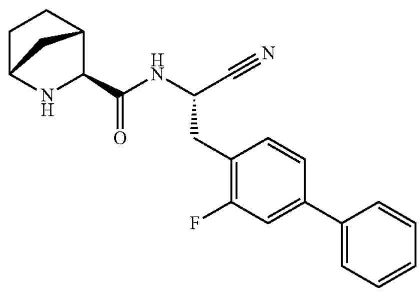
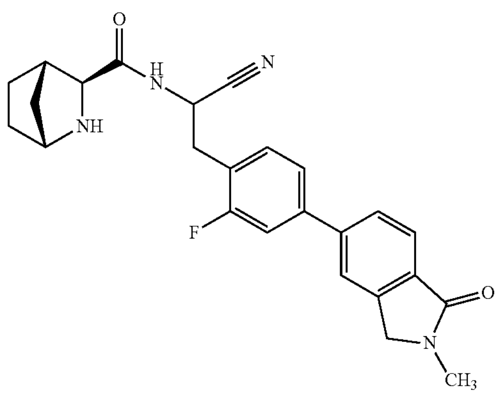
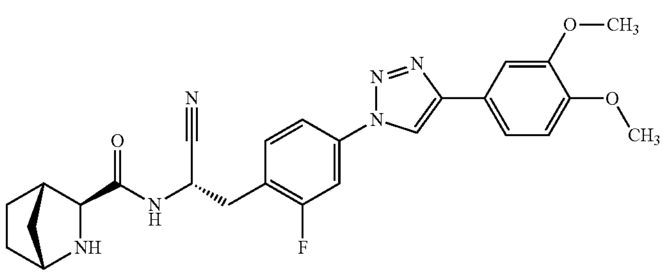
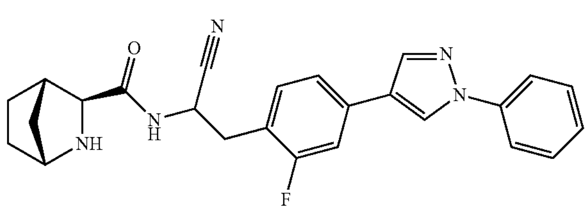
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
74		I-2.3.7.9	A1/TSA	41
75		I-3.3.4	A2.1/SI	4
76		I-4.3.22	A3/FA	89
77		I-5.2	A4/TSA	40
78		I-2.3.27	A1/TSA	7

TABLE 62-continued

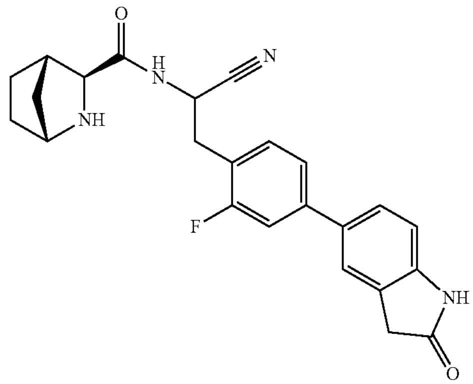
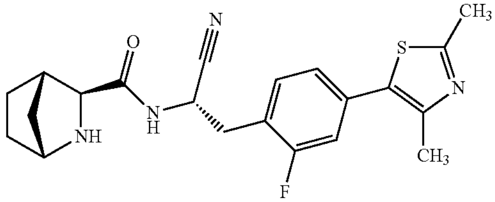
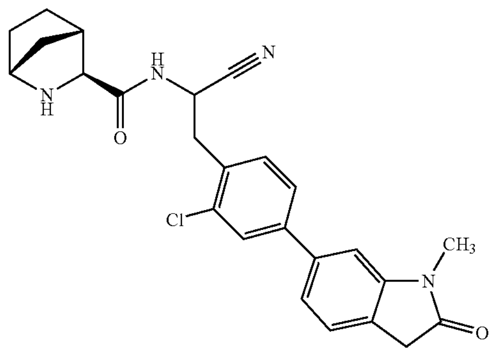
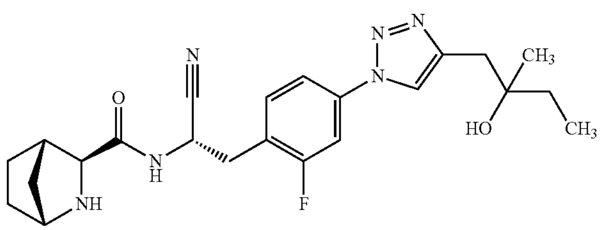
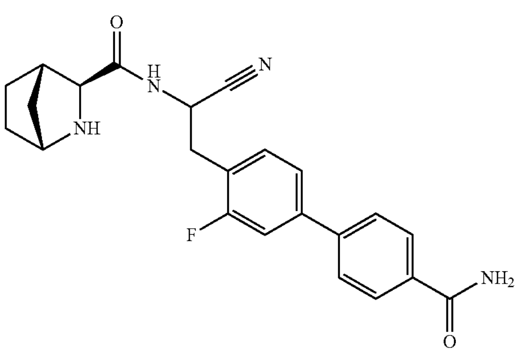
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
79		I-4.3.23	A3/FA	80
80		I-2.3.28	A1/TSA	24
81		I-4.3.24	A3/SI	31
82		I-5.2	A4/TSA	44
83		I-4.3.25	A3/FA	>95

TABLE 62-continued

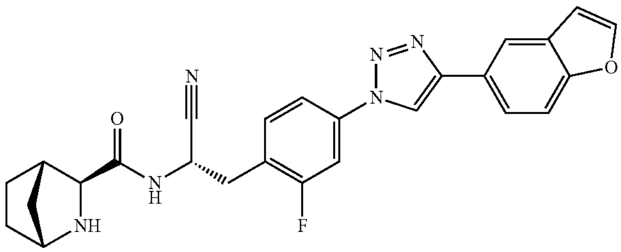
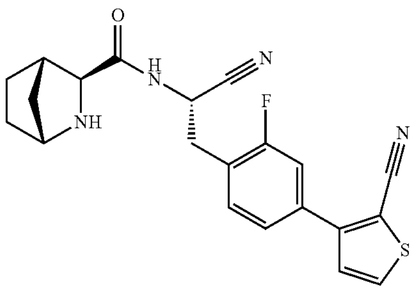
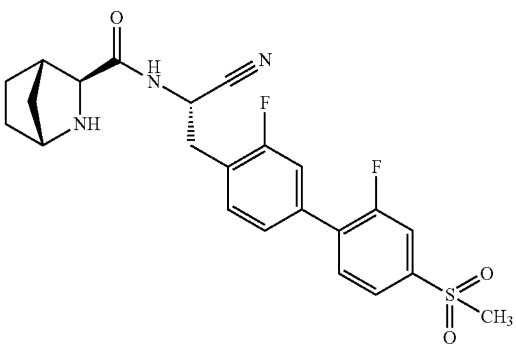
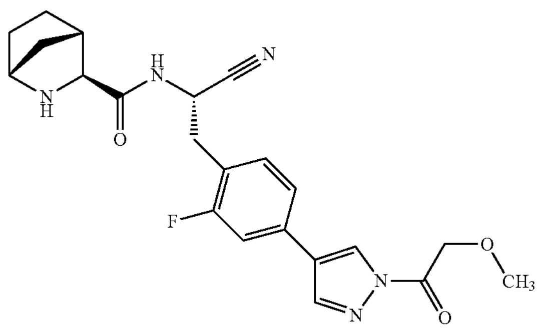
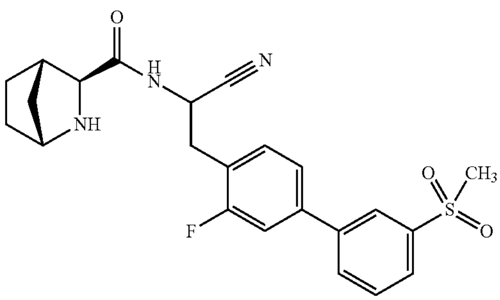
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
84		I-5.2	A4/TSA	46
85		I-2.3.29	A1/FA	60
86		I-2.3.30	A1/FA	63
87		I-2.3.7.10	A1/TSA	8
88		I-4.3.26	A3/FA	52

TABLE 62-continued

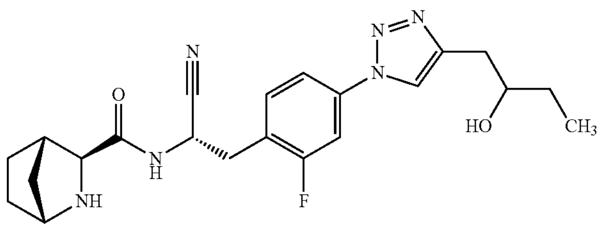
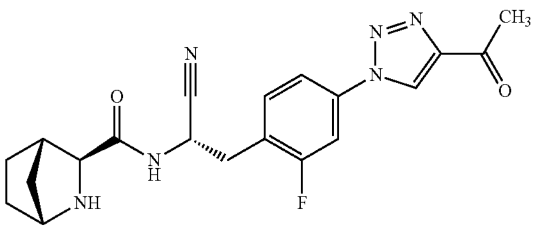
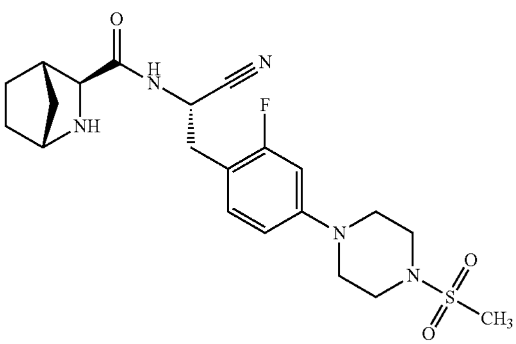
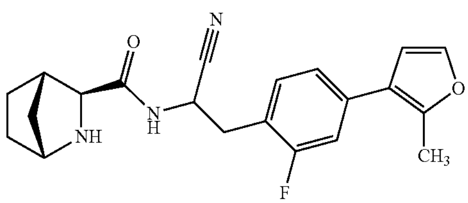
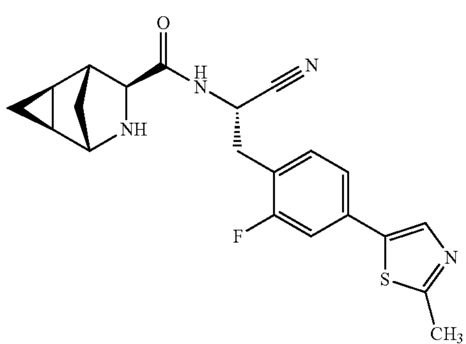
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
89		I-5.2	A4/TSA	48
90		I-5.2	A4/TSA	77
91		I-3.2.9	A2.2/TSA	92
92		I-2.3.31	A1/TSA	14
93		I-2.3.32	A1/TSA	54

TABLE 62-continued

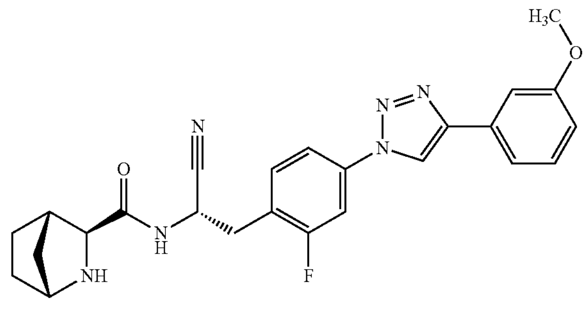
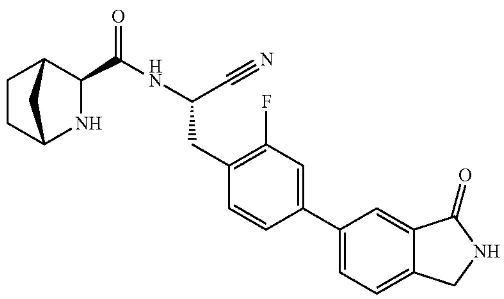
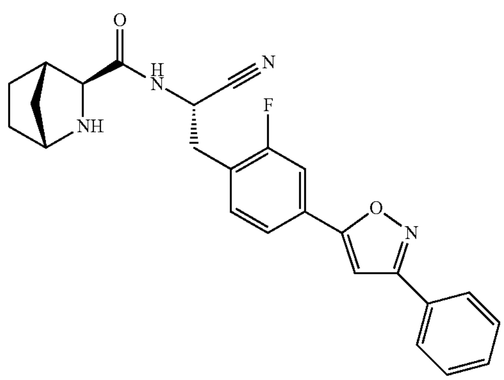
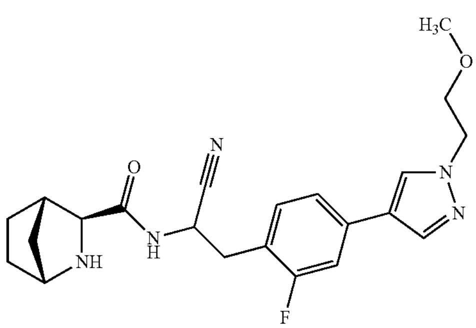
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
94		I-5.2	A4/TSA	80
95		I-3.2.10	A2.1/TSA	53
96		I-2.3.33	A1/FA	87
97		I-2.3.34	A1/TSA	22

TABLE 62-continued

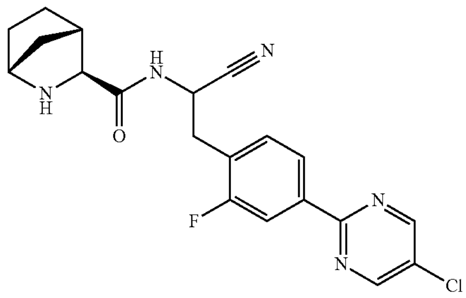
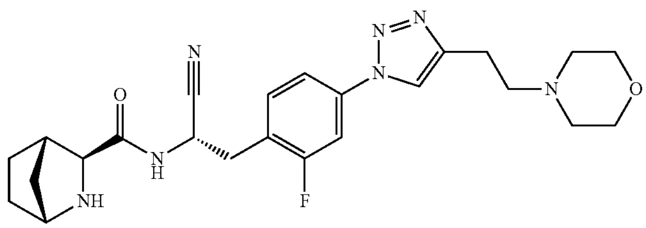
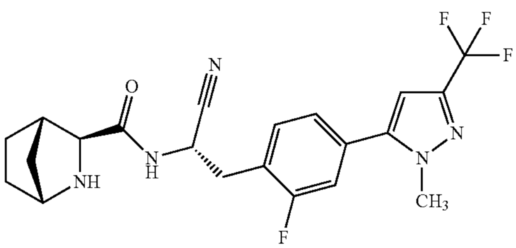
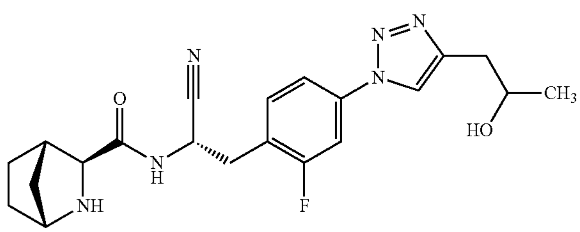
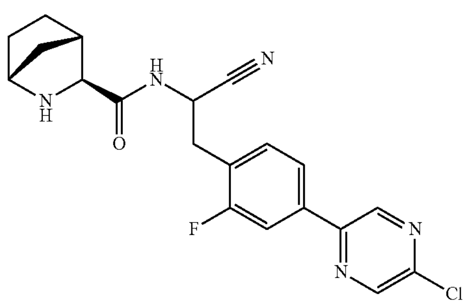
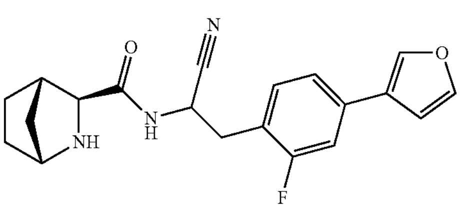
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
98		I-3.2.11	A2.1/SI	83
99		I-5.2	A4/TSA	34
100		I-2.3.35	A1/TSA	16
101		I-5.2	A4/TSA	48
102		I-3.2.12	A2.1/SI	29
103		I-2.3.36	A1/TSA	17

TABLE 62-continued

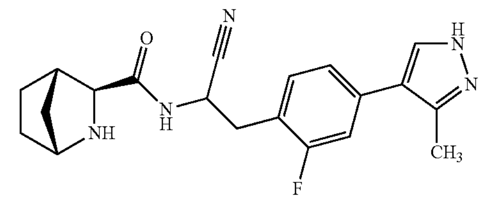
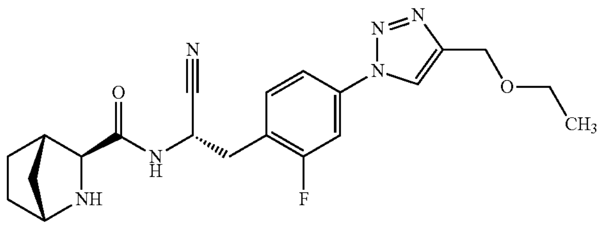
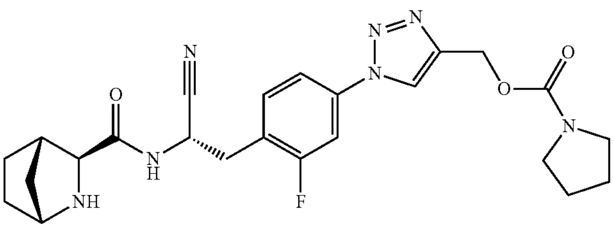
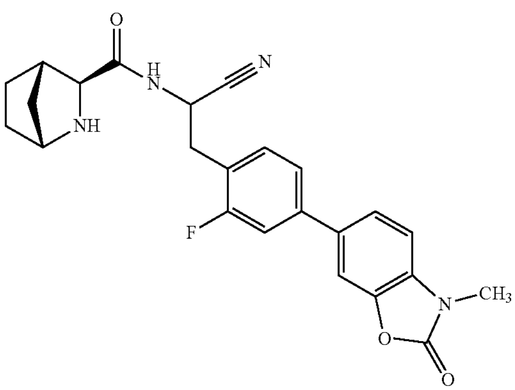
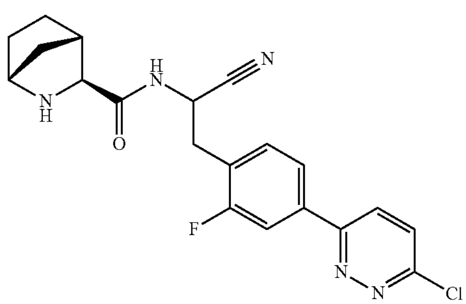
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
104		I-2.3.37	A1/TSA	8
105		I-5.2	A4/TSA/TSA	26
106		I-5.2	A4/TSA	30
107		I-4.3.27	A3/FA	80
108		I-3.2.13	A2.1/SI	42

TABLE 62-continued

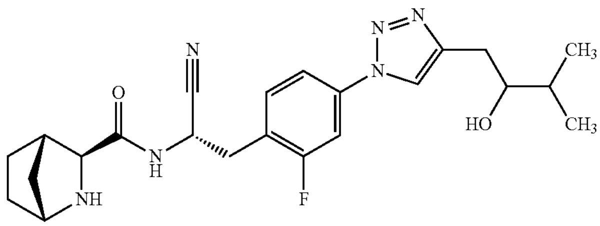
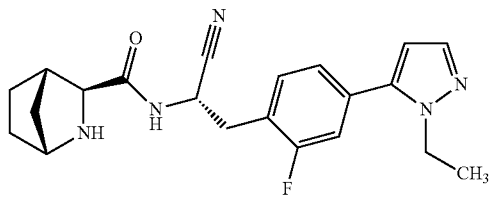
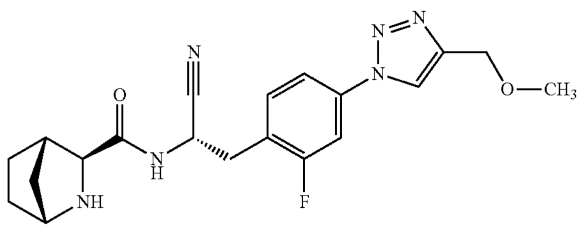
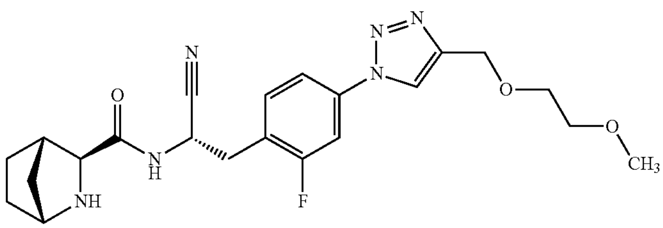
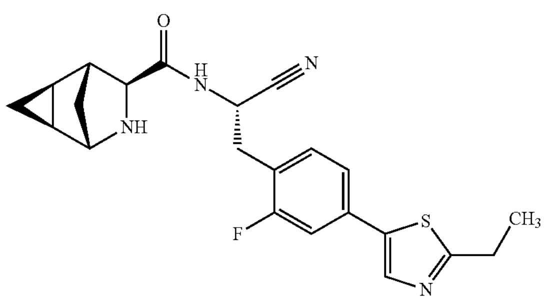
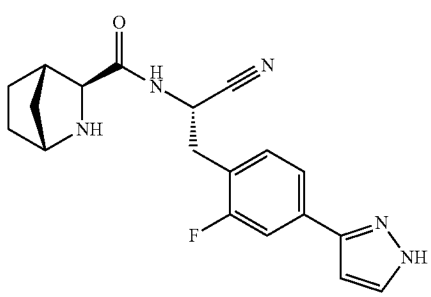
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
109		I-5.2	A4/TSA	41
110		I-2.3.38	A1/TSA	21
111		I-5.2	A4/TSA	84
112		I-5.2	A4/TSA	22
113		I-2.3.39	A1/TSA	45
114		I-2.3.40	A1/TSA	53

TABLE 62-continued

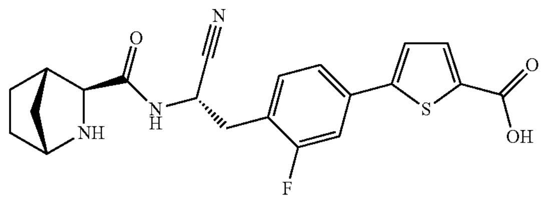
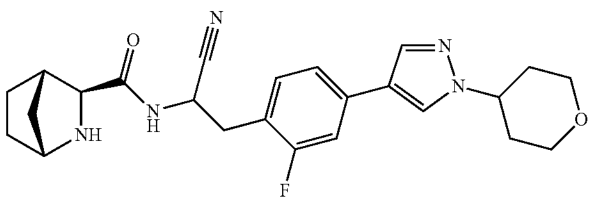
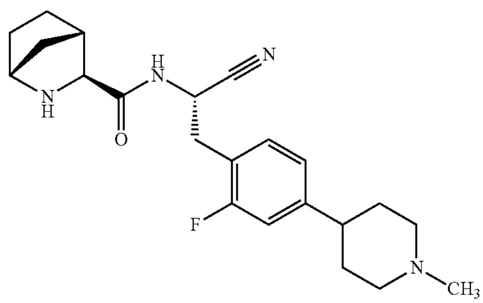
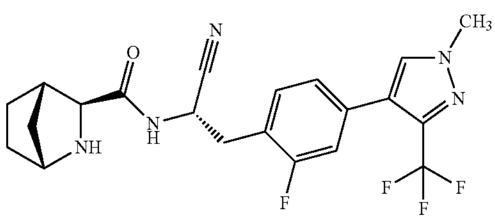
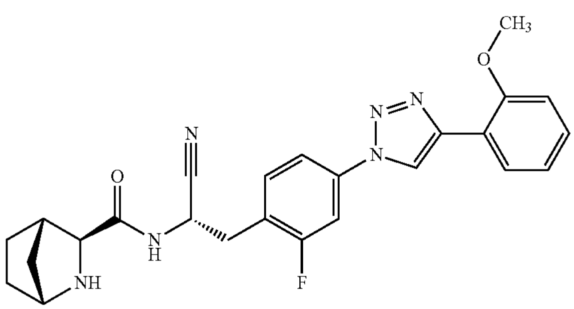
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
115		I-2.3.41	A1/TSA	30
116		I-2.3.42	A1/TSA	8
117		I-2.3.43.1	A1/SI	57
118		I-2.3.44	A1/TSA	40
119		I-5.2	A4/TSA	37

TABLE 62-continued

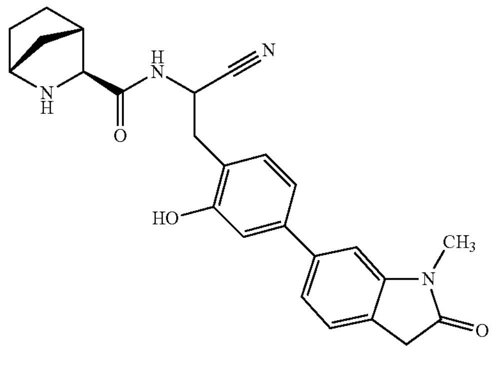
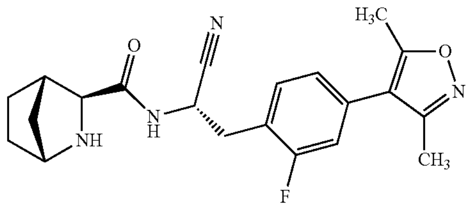
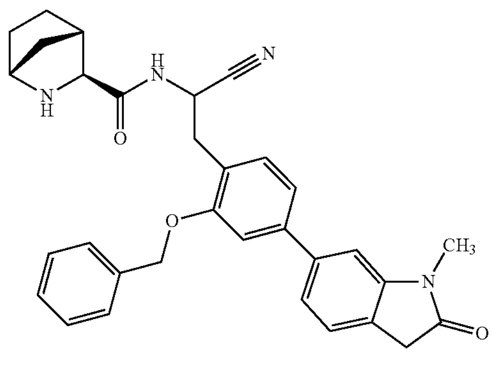
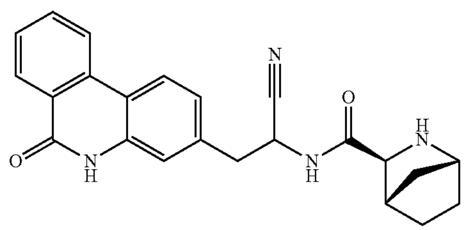
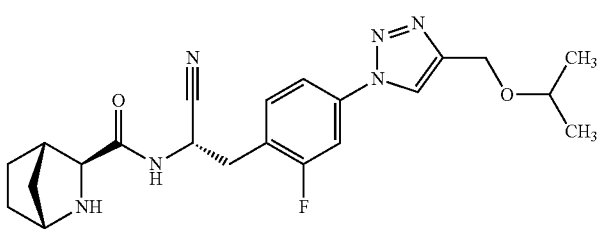
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
120		I-4.3.19	A3/SI	5
121		I-2.3.45	A1/TSA	41
122		I-4.3.19	A3/SI	27
123		I-10.5	E/FA	10
124		I-5.2	A4/TSA	36

TABLE 62-continued

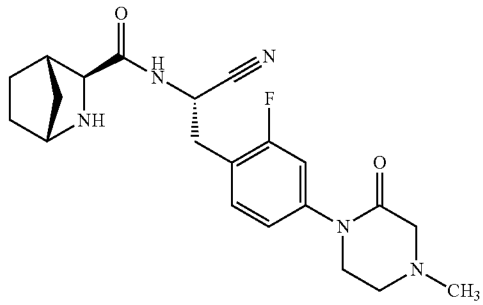
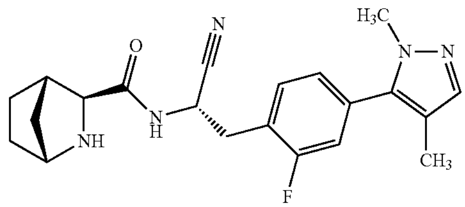
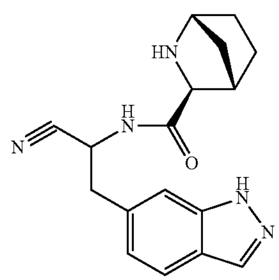
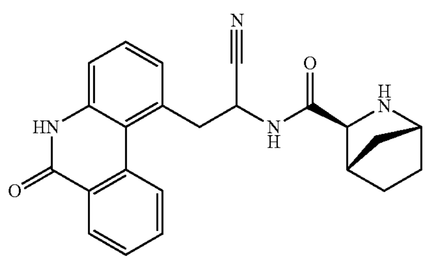
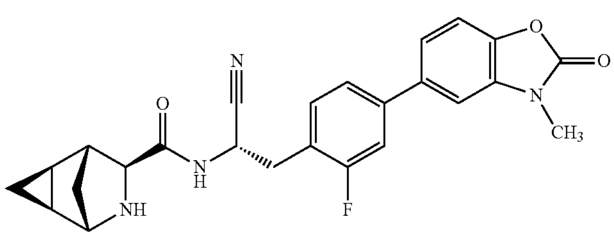
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
125		I-4.3.28	A3/TSA	79
126		I-2.3.46	A1/TSA	7
127		I-8.2.1	C/SI	36
128		I-10.5	E/FA	5
129		I-2.3.47	A1/TSA	21

TABLE 62-continued

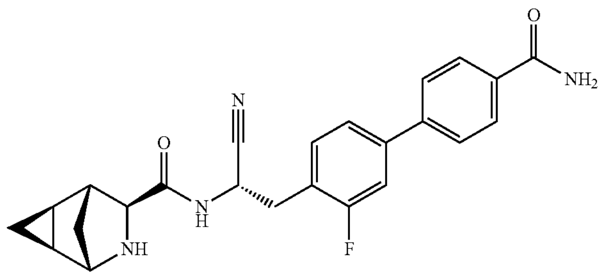
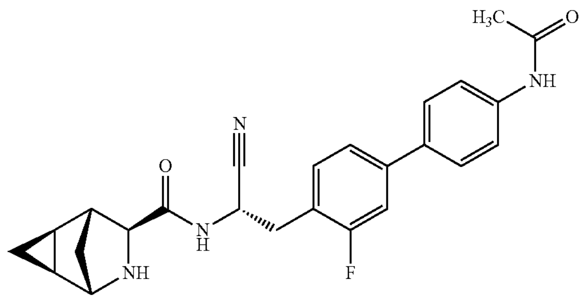
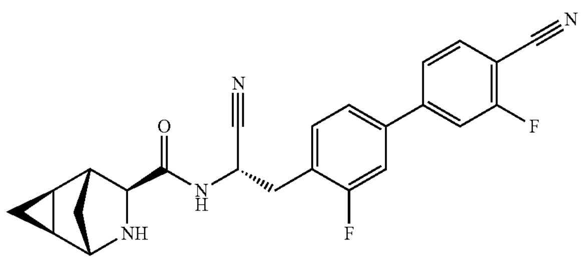
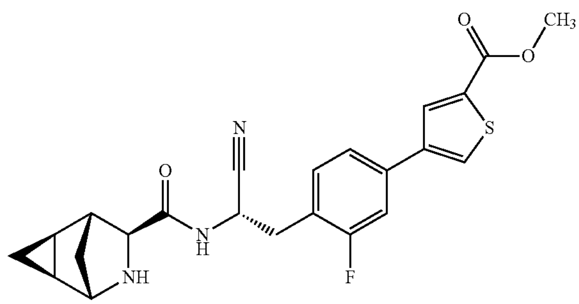
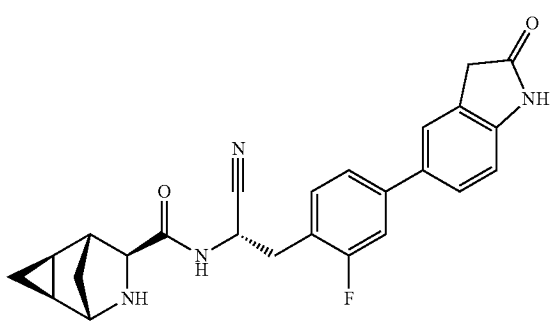
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
130		I-2.3.48	A1/TSA	33
131		I-2.3.49	A1/TSA	28
132		I-2.3.50	A1/TSA	36
133		I-2.3.51	A1/TSA	28
134		I-2.3.52	A1/TSA	8

TABLE 62-continued

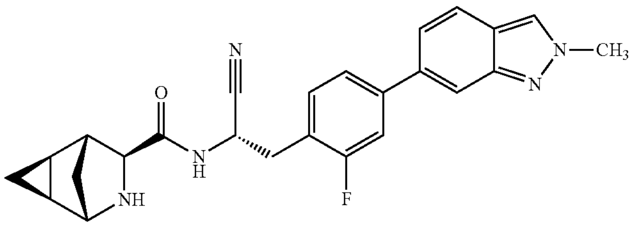
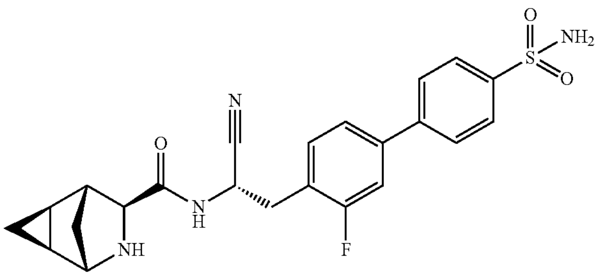
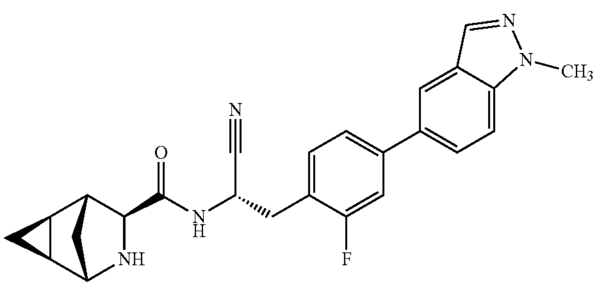
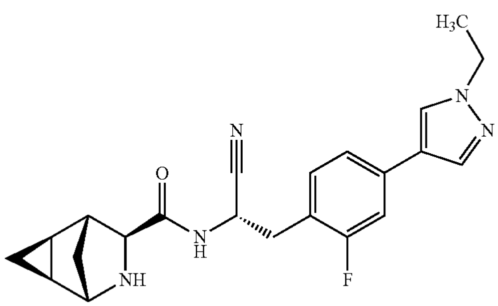
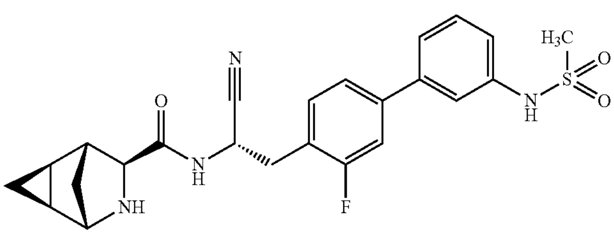
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
135		I-2.3.53	A1/TSA	25
136		I-2.3.54	A1/TSA	33
137		I-2.3.55	A1/TSA	25
138		I-2.3.56	A1/TSA	41
139		I-2.3.57	A1/TSA	26

TABLE 62-continued

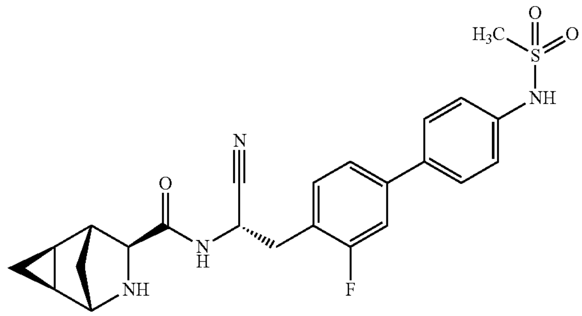
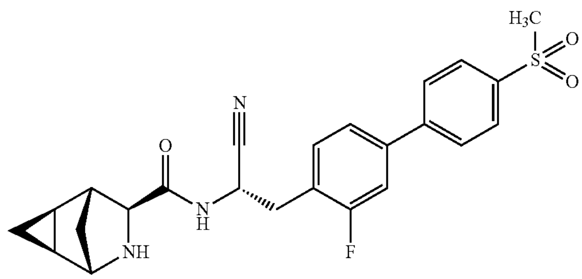
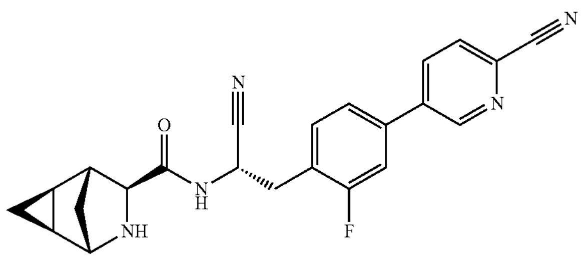
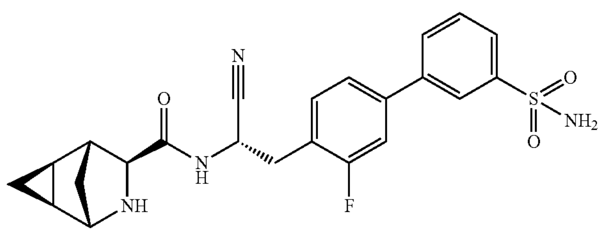
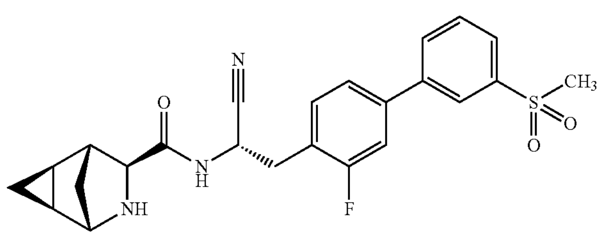
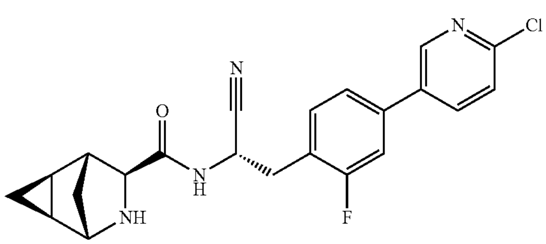
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
140		I-2.3.58	A1/TSA	16
141		I-2.3.59	A1/TSA	28
142		I-2.3.60	A1/TSA	24
143		I-2.3.61	A1/TSA	33
144		I-2.3.62	A1/TSA	34
145		I-2.3.63	A1/TSA	21

TABLE 62-continued

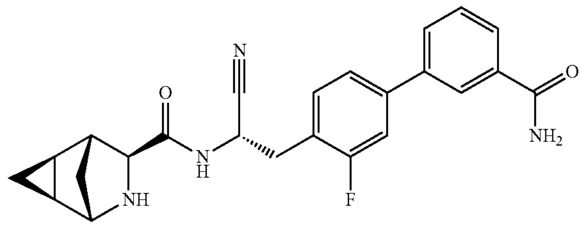
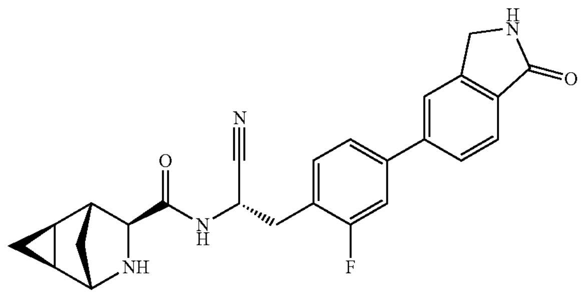
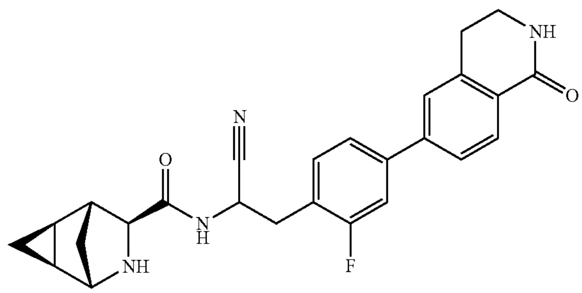
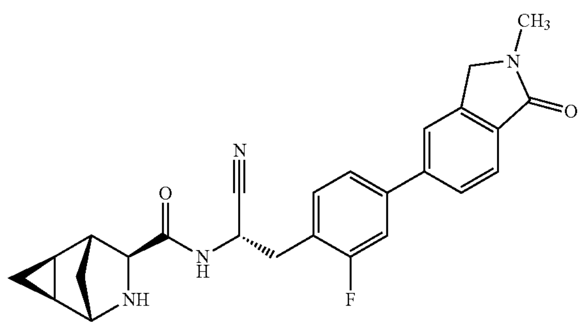
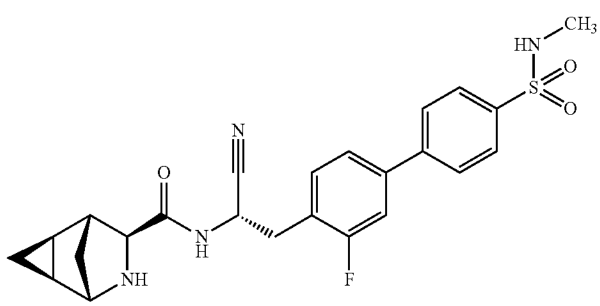
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
146		I-2.3.64	A1/TSA	32
147		I-2.3.65	A1/TSA	34
148		I-2.3.66	A1/TSA	10
149		I-2.3.67	A1/TSA	23
150		I-2.3.68	A1/TSA	33

TABLE 62-continued

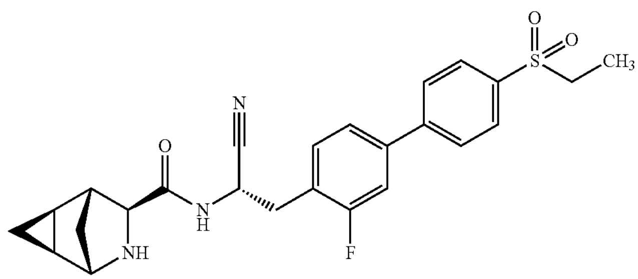
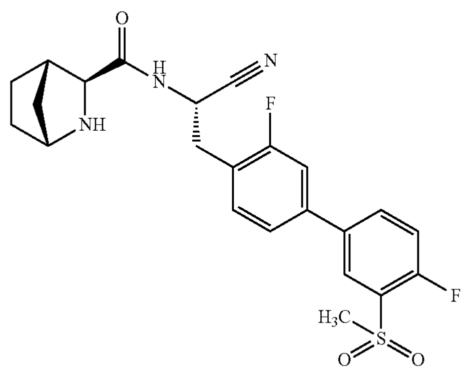
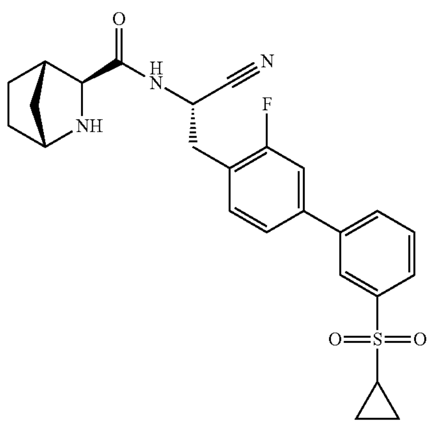
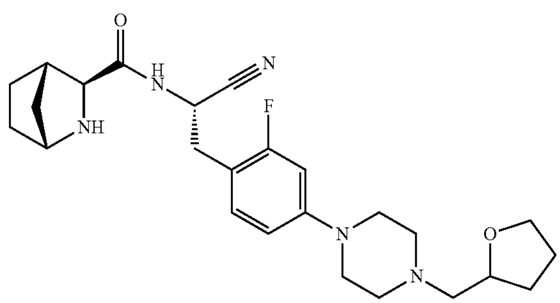
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
151		I-2.3.69	A1/TSA	25
152		I-2.3.70	A1/FA	68
153		I-2.3.71	A1/FA	73
154		I-3.2.14	A2.2/TSA	59

TABLE 62-continued

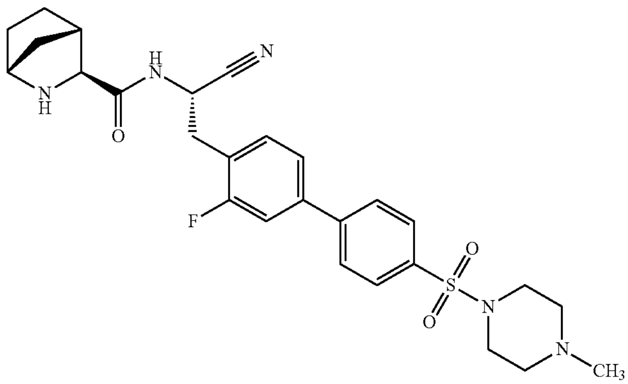
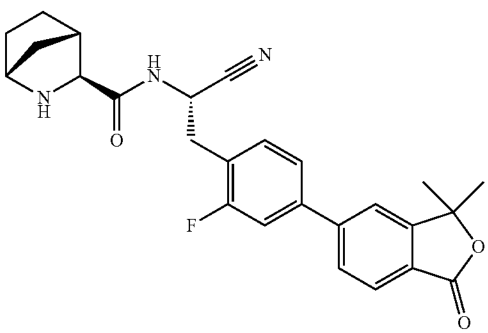
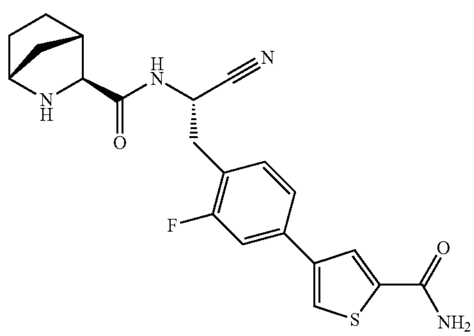
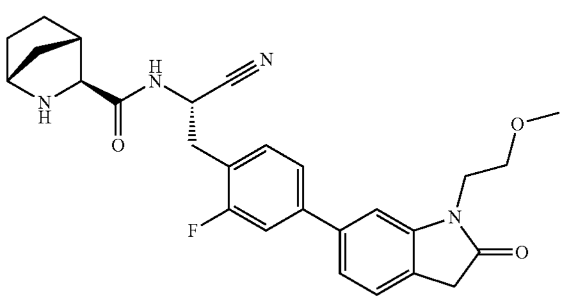
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
155		I-3.3.5	A2.1/SI	62
156		I-3.3.6	A2.1/SI	25
157		I-4.3.32	A3/FA	36
158		I-2.3.72	A1/SI	57

TABLE 62-continued

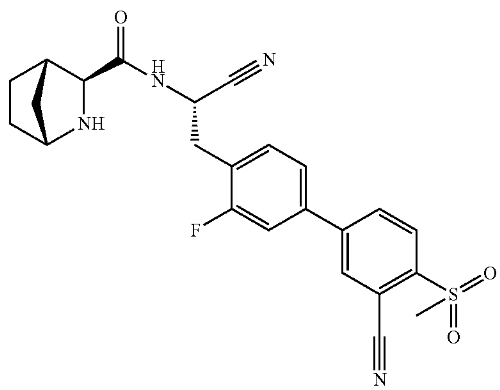
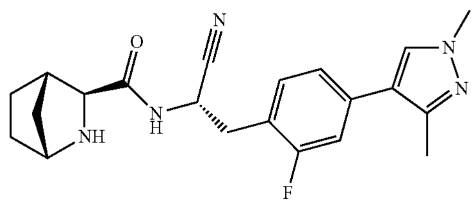
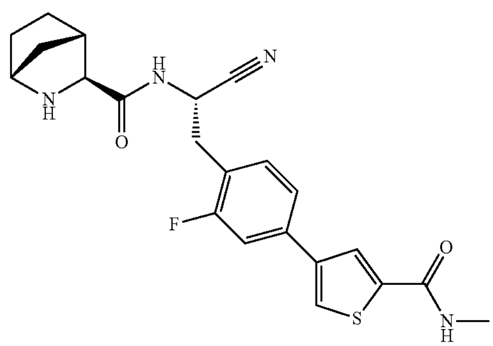
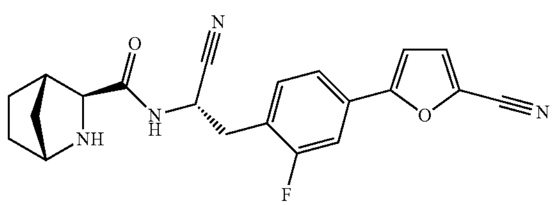
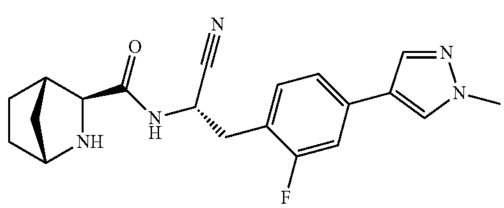
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
159		I-1.5.1	A/TSA	65
160		I-3.2.37	A2.1/TSA	34
161		I-4.3.33	A3/FA	75
162		I-3.2.47	A2.1/TSA	52
163		I-3.2.36	A2.1/TSA	40

TABLE 62-continued

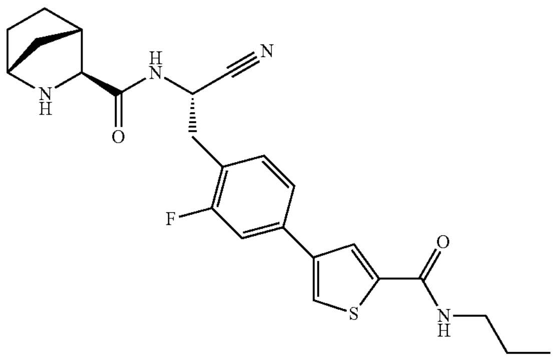
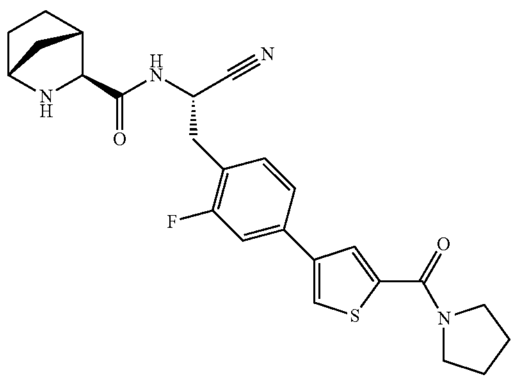
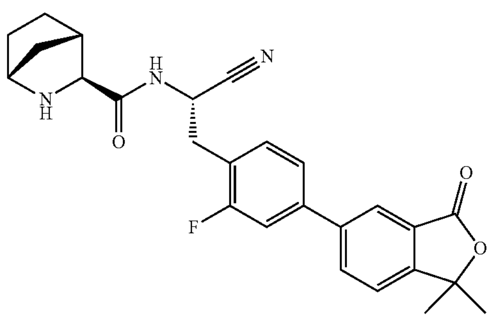
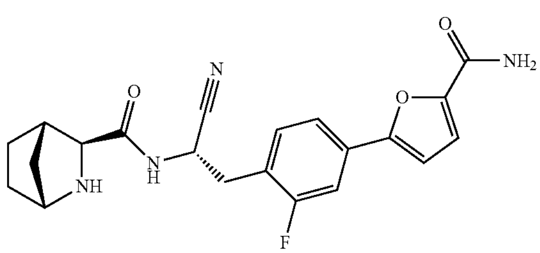
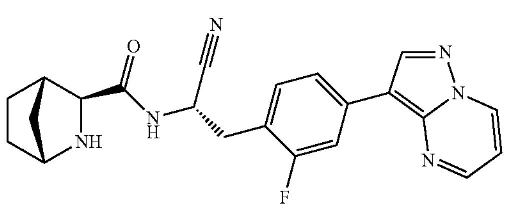
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
164		I-4.3.34	A3/FA	78
165		I-4.3.35	A3/FA	90
166		I-3.3.7	A2.1/SI	33
167		I-3.2.46	A2.1/TSA	49
168		I-3.2.42	A2.1/TSA	37

TABLE 62-continued

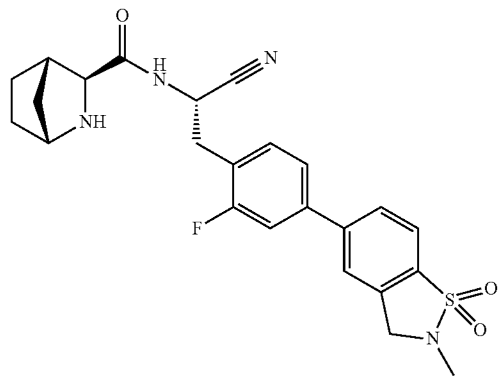
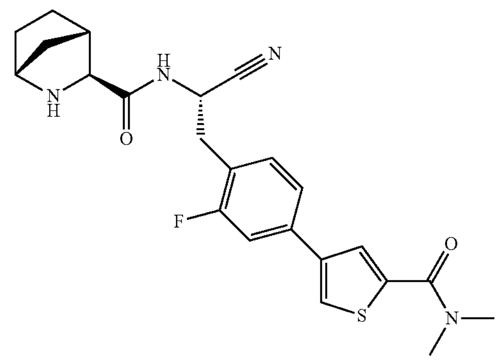
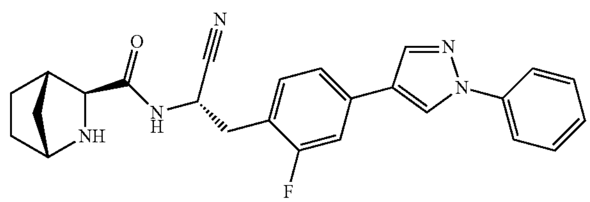
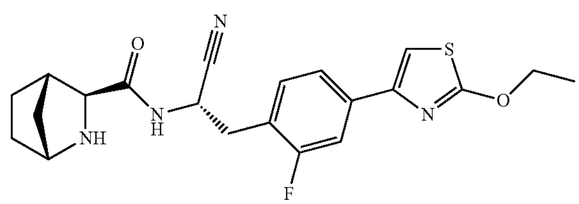
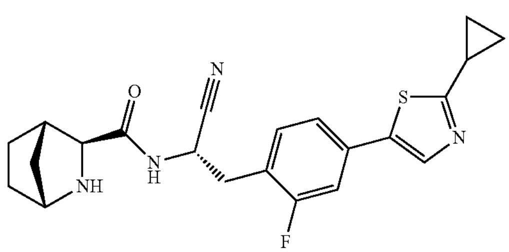
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
169		I-1.5.2	A/TSA	79
170		I-4.3.36	A3/FA	77
171		I-3.2.39	A2.1/TSA	37
172		I-3.2.38	A2.1/TSA	36
173		I-3.2.45	A2.1/TSA	34

TABLE 62-continued

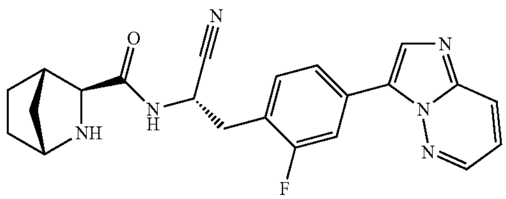
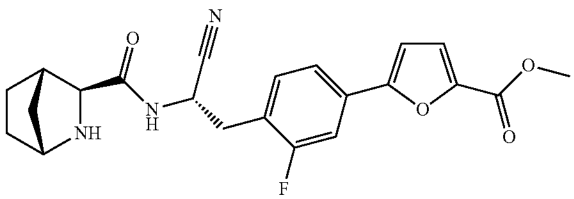
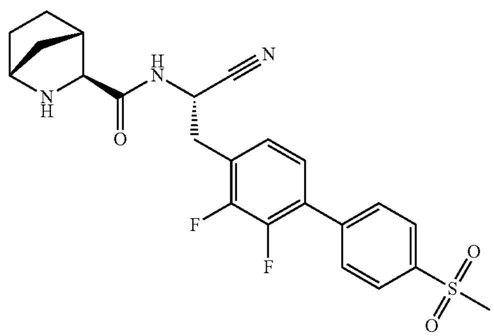
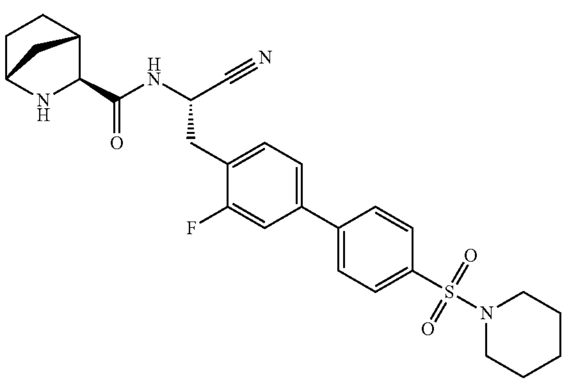
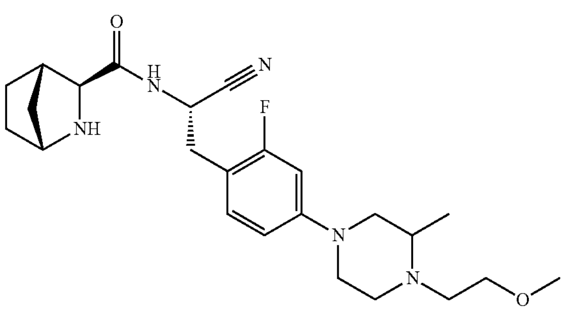
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
174		I-3.2.40	A2.1/TSA	33
175		I-3.2.50	A2.1/TSA	44
176		I-2.3.75.1	A1/FA	53
177		I-3.2.51	A2.1/SI	59
178		I-3.2.19	A2.2/TSA	81

TABLE 62-continued

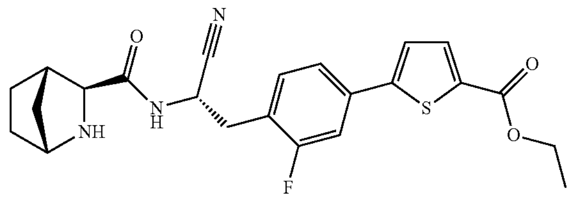
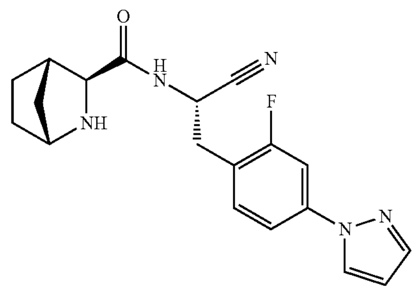
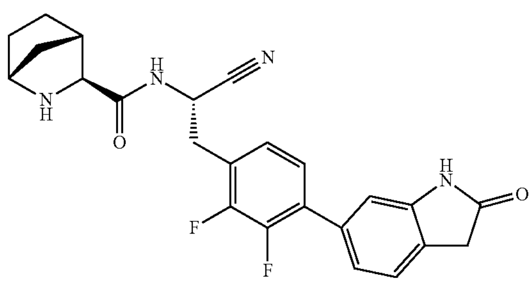
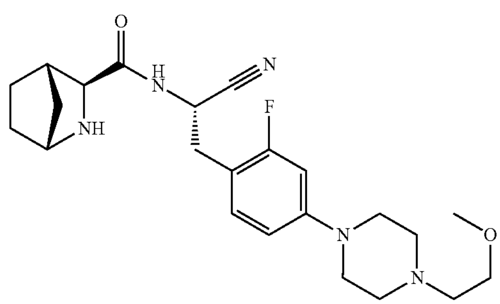
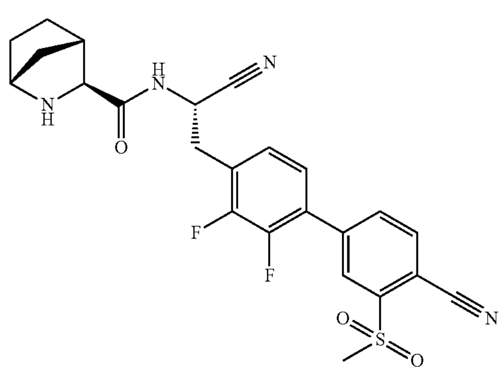
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
179		I-3.2.49	A2.1/TSA	35
180		I-3.2.20	A2.2/TSA	56
181		I-2.3.76.1	A1/FA	31
182		I-3.2.22	A2.2/TSA	31
183		I-2.3.78.1	A1/FA	36

TABLE 62-continued

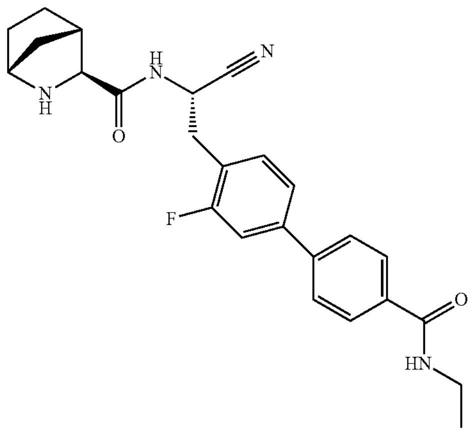
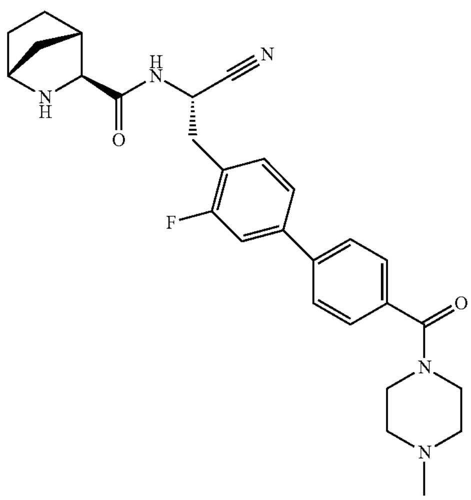
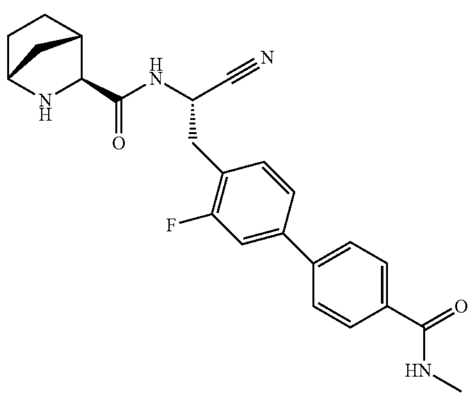
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
184		I-4.3.37	A3/TFA	51
185		I-4.3.38	A3/TFA	28
186		I-4.3.39	A3/TFA	40

TABLE 62-continued

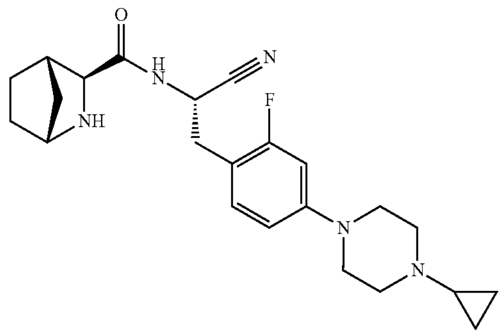
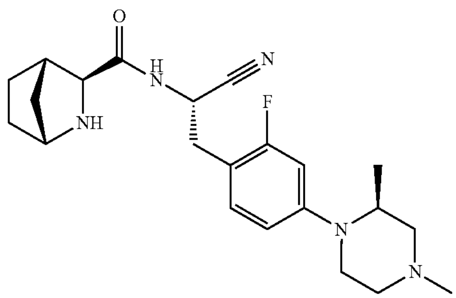
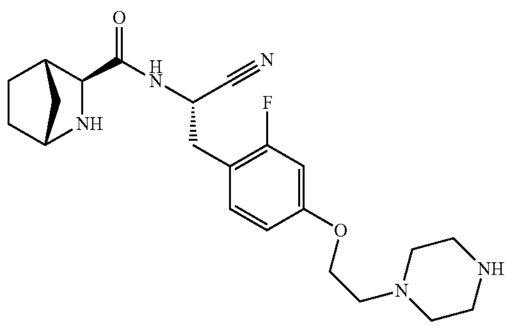
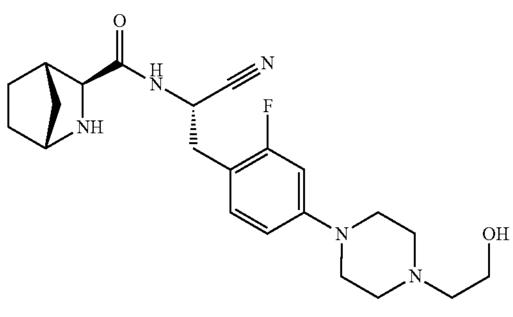
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
187		I-3.2.24	A2.2/SI	17
188		I-3.2.25	A2.2/TSA	85
189		I-3.2.26	A2.2/TSA	13
190		I-3.2.27	A2.2.TSA	19

TABLE 62-continued

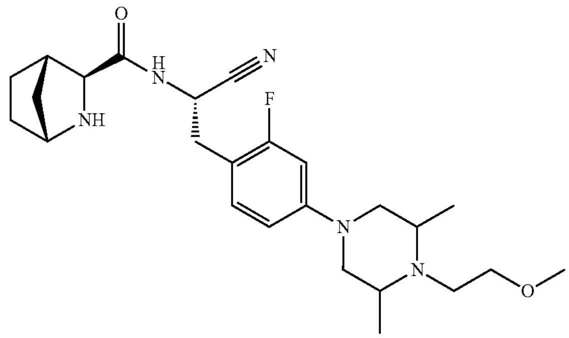
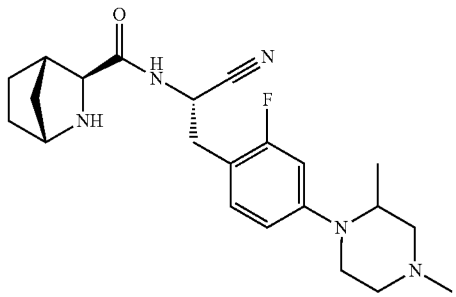
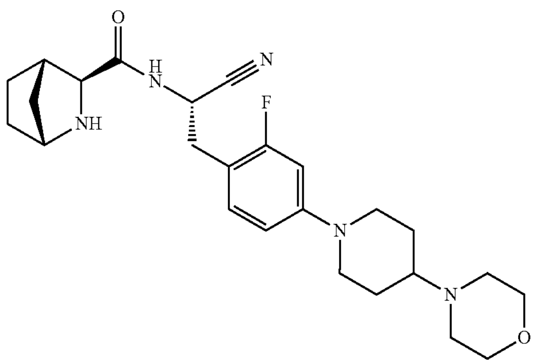
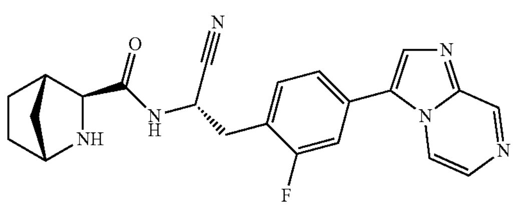
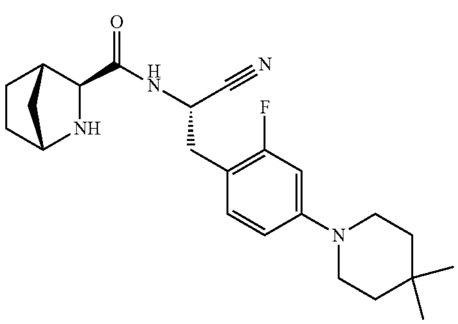
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
191		I-3.2.28	A2.2/TSA	84
192		I-3.2.29	A2.2/TSA	75
193		I-3.2.30	A2.2/TSA	42
194		I-3.2.41	A2.1/TSA	33
195		I-3.2.31	A2.2/TSA	86

TABLE 62-continued

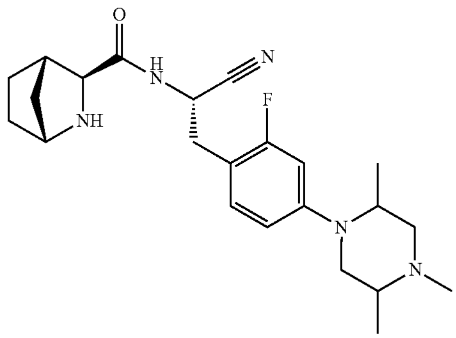
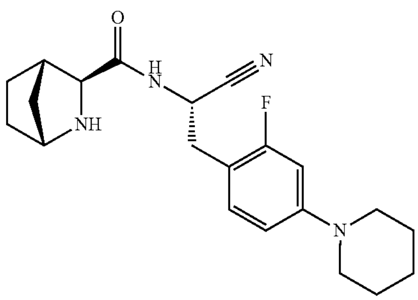
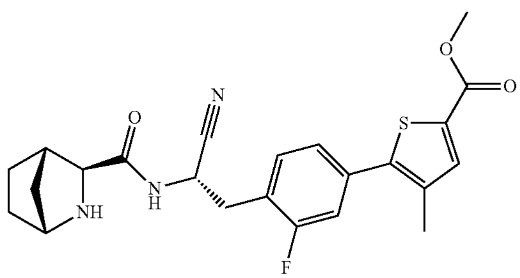
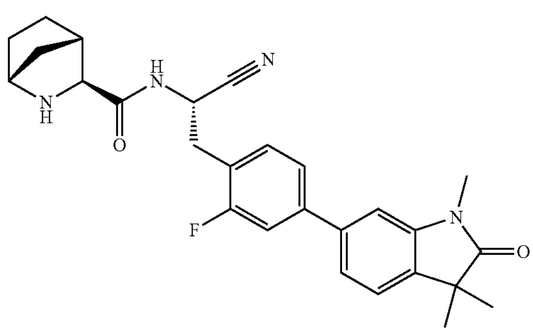
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
196		I-3.2.32	A2.2/TSA	18
197		I-3.2.33	A2.2/TSA	68
198		I-3.2.48	A2.1/TSA	32
199		I-2.3.73	A1/SI	56

TABLE 62-continued

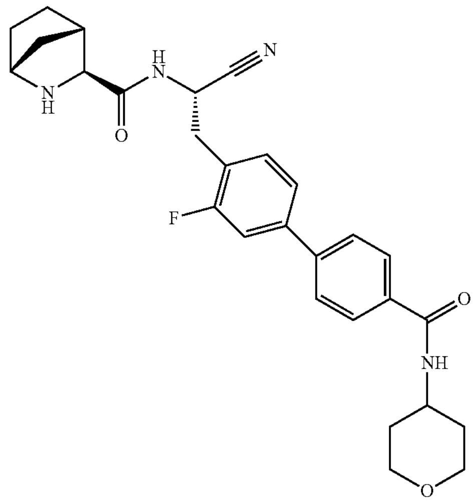
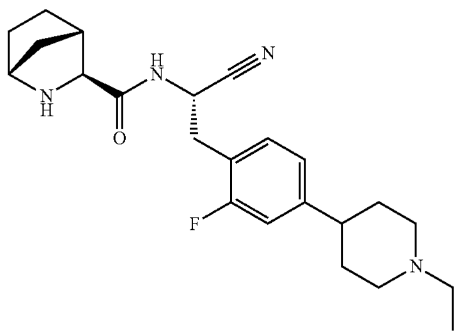
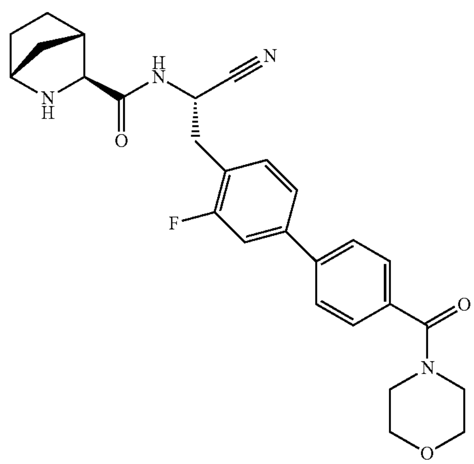
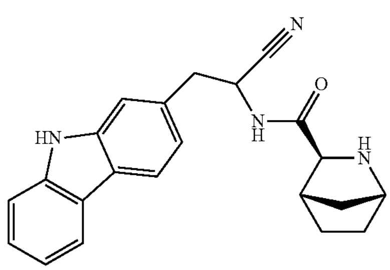
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
200		I-4.3.40	A3/TFA	51
201		I-2.3.43.2.1	A2/SI	65
202		I-4.3.41	A3/TFA	52
203		I-7.3.3	B/SI	56

TABLE 62-continued

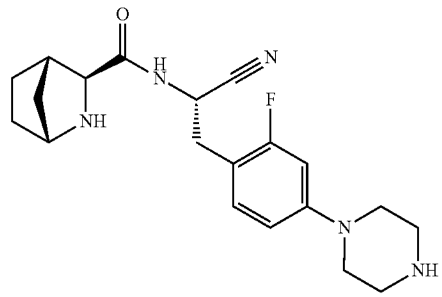
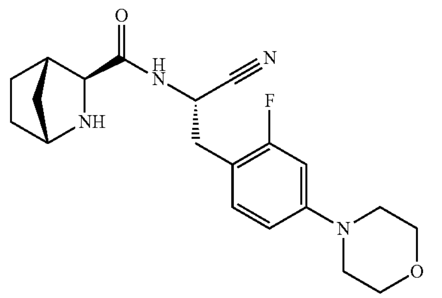
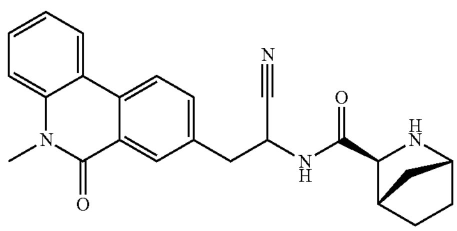
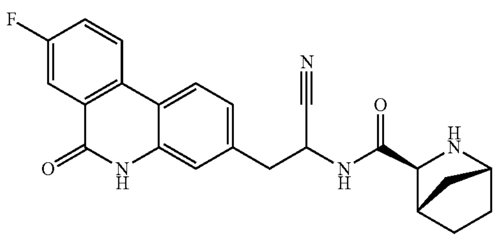
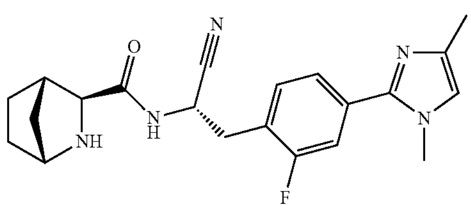
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
204		I-3.2.34	A2.2/TSA	90
205		I-3.2.35	A2.2/TSA	76
206		I-9.1.1	D/SI	39
207		I-10.4.1	E/TFA	28
208		I-3.2.43	A2.1/TSA	22

TABLE 62-continued

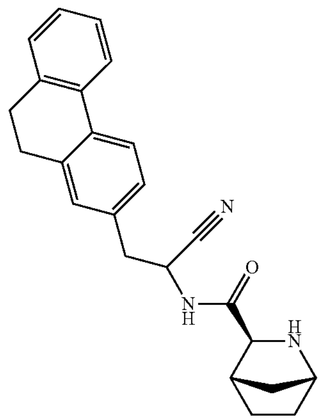
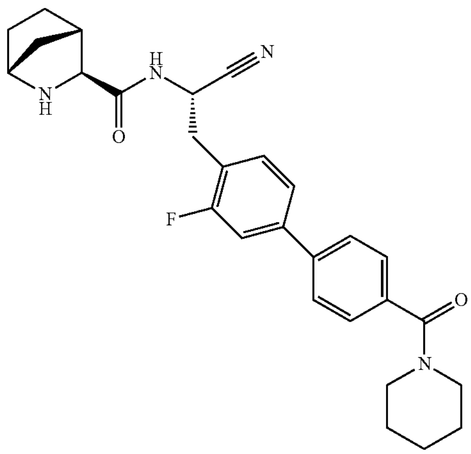
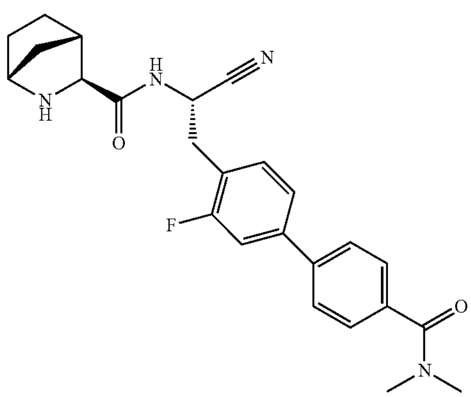
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
209		I-7.3.4	B/SI	55
210		I-4.3.42	A3/TFA	46
211		I-4.3.43	A3/TFA	48

TABLE 62-continued

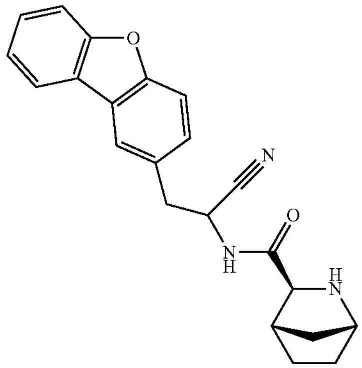
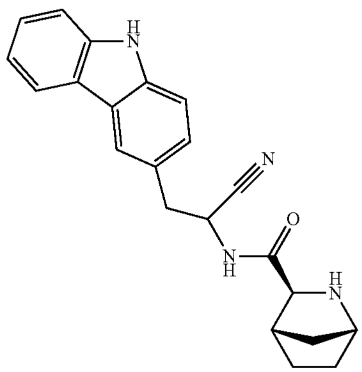
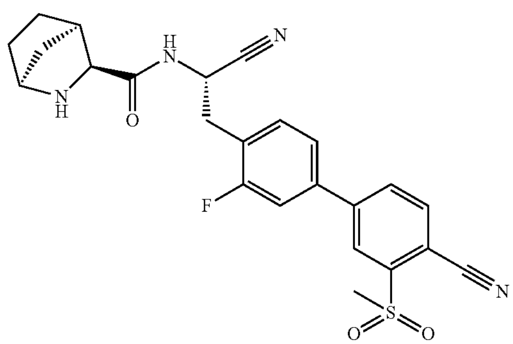
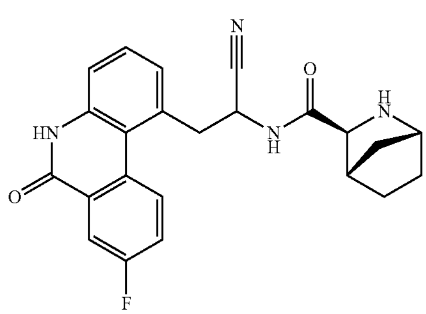
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
212		I-7.3.5	B/SI	54
213		I-7.3.6	B/SI	65
214		I-1.5.3	A/TSA	72
215		I-10.4.1	E/TFA	23

TABLE 62-continued

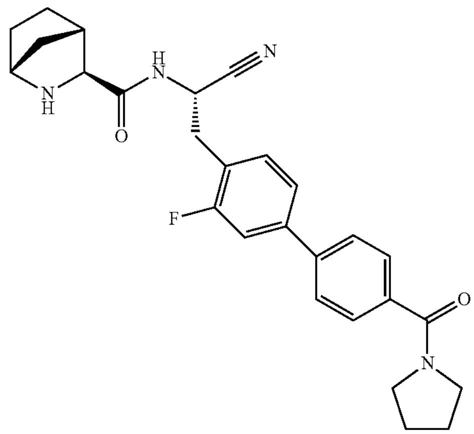
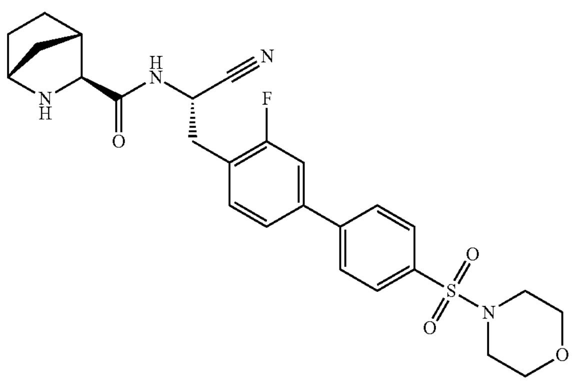
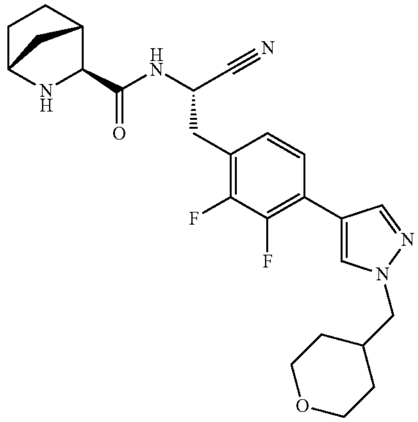
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
216		I-4.3.44	A3/TFA	38
217		I-3.2.52	A2.1/SI	64
218		I-2.3.77.1	A1/FA	24

TABLE 62-continued

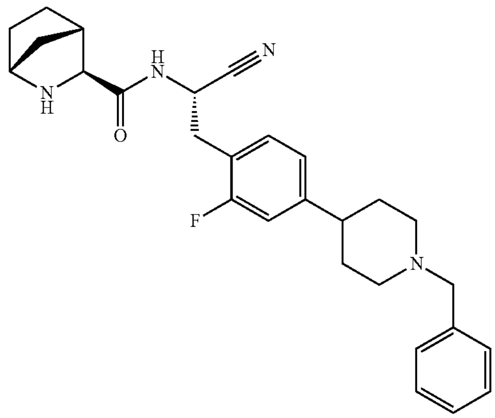
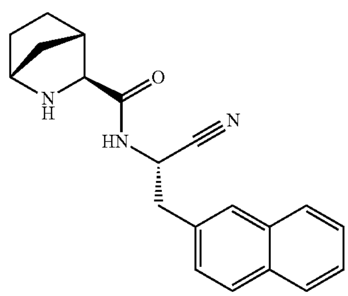
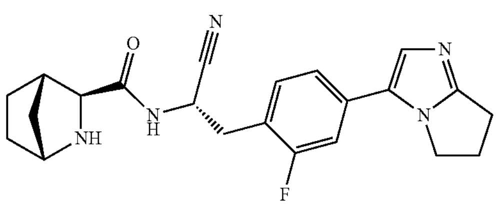
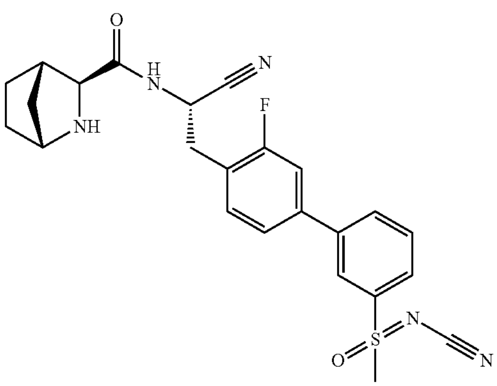
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
219		I-2.3.43.3	A1/SI	41
220		I-8.2.2	C/SI	69
221		I-3.2.44	A2.1/TSA	17
222		I-3.2.53	A2.1/FA	59

TABLE 62-continued

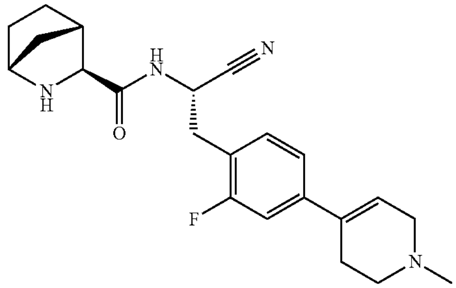
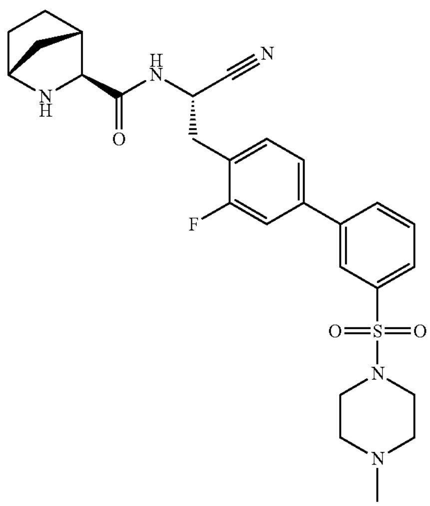
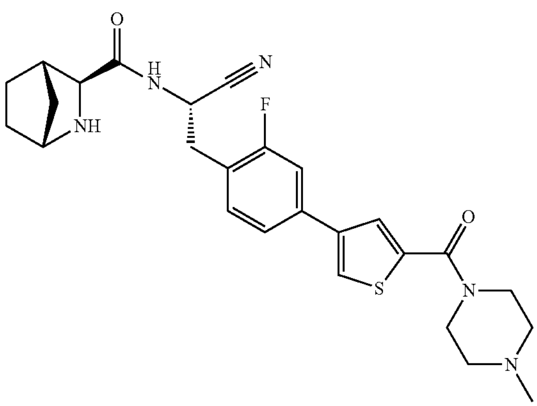
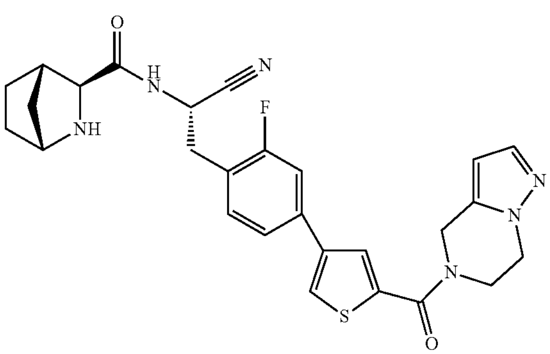
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
223		I-2.3.43	A1/SI	60
224		I-2.3.79	A1/SI	47
225		I-4.3.45	A3/FA	15
226		I-4.3.46	A3/FA	53

TABLE 62-continued

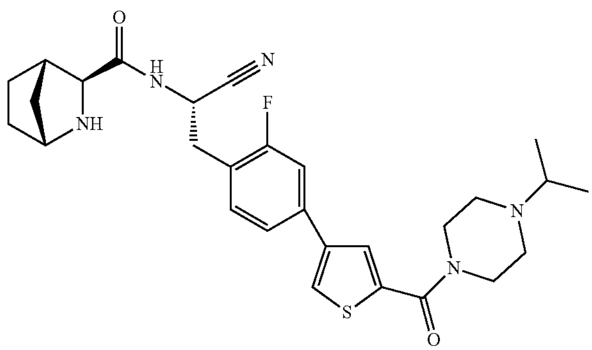
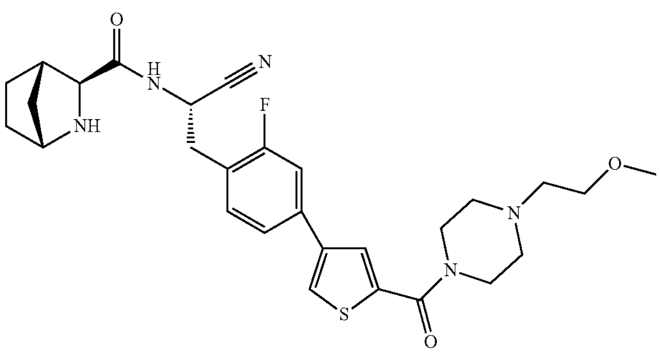
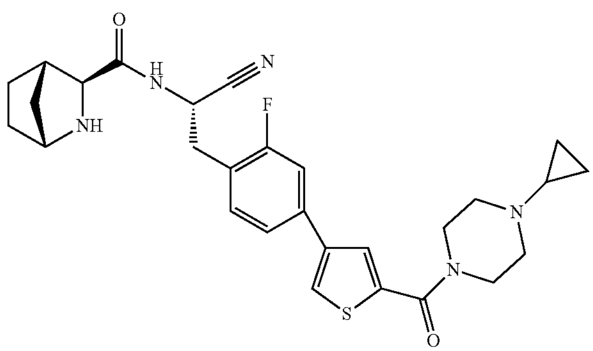
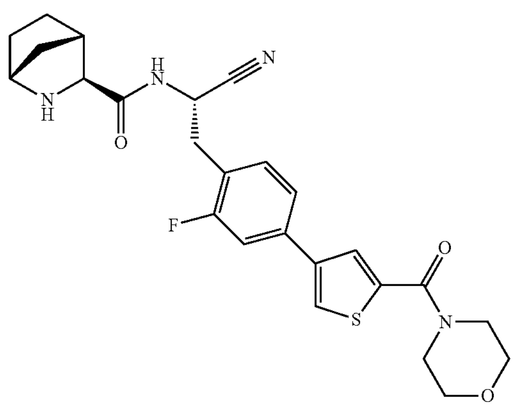
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
227		I -4.3.47	A3/FA	28
228		I-4.3.48	A3/FA	37
229		I-4.3.49	A3/FA	14
230		I-4.3.50	A3/FA	47

TABLE 62-continued

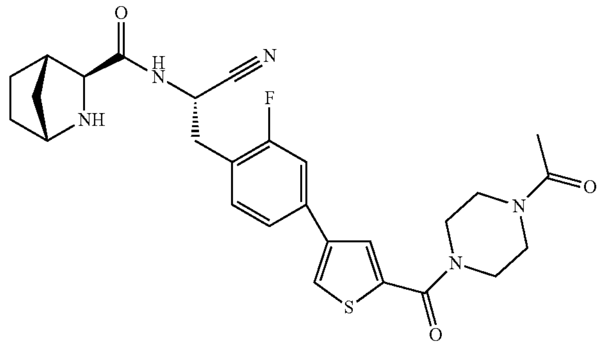
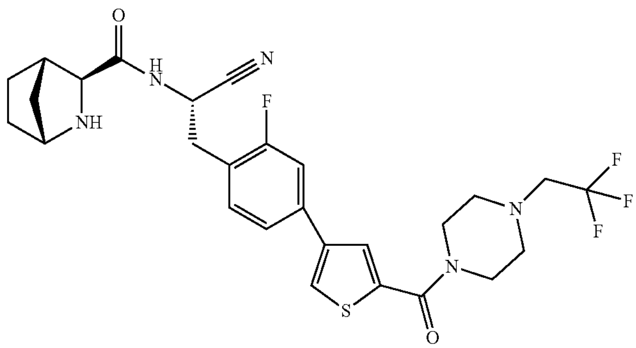
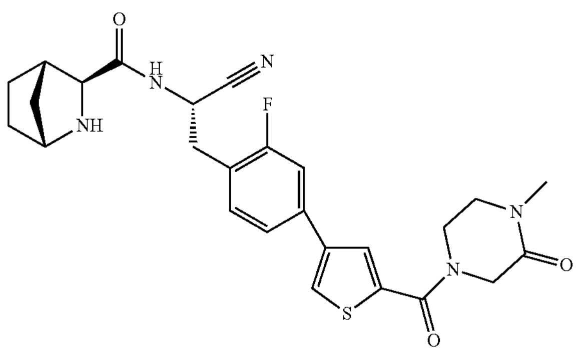
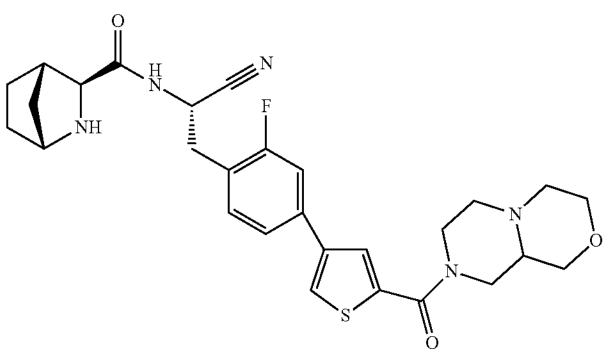
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
231		I-4.3.51	A3/FA	30
232		I-4.3.52	A3/FA	60
233		I-4.3.53	A3/FA	37
234		I-4.3.54	A3/FA	71

TABLE 62-continued

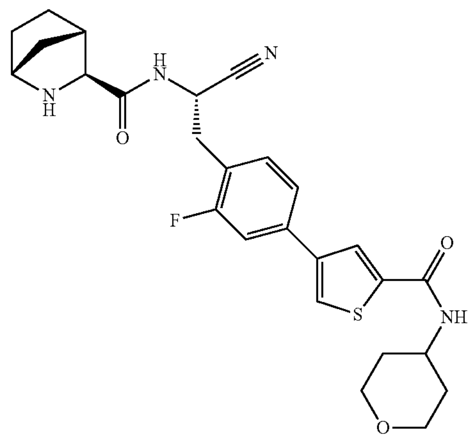
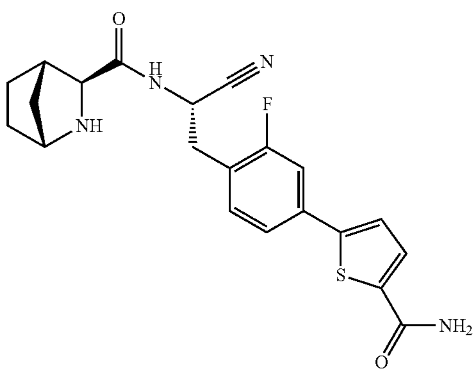
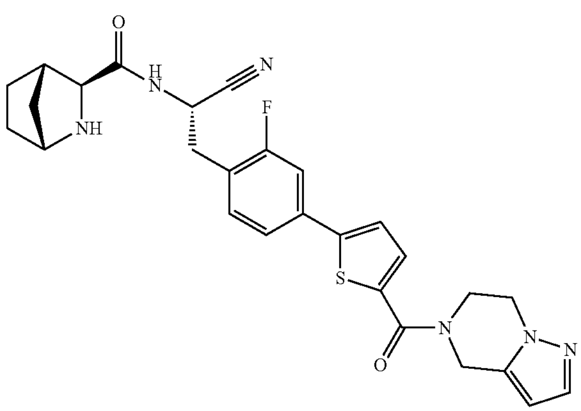
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
235		I-4.3.55	A3/FA	38
236		I-4.3.56	A1/FA	41
237		I-4.3.57	A1/TSA	67

TABLE 62-continued

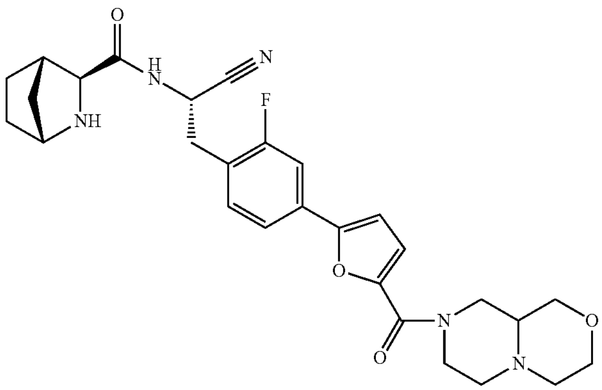
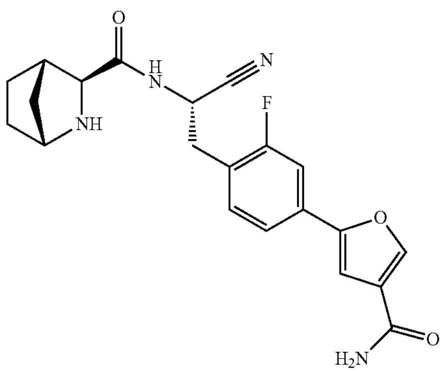
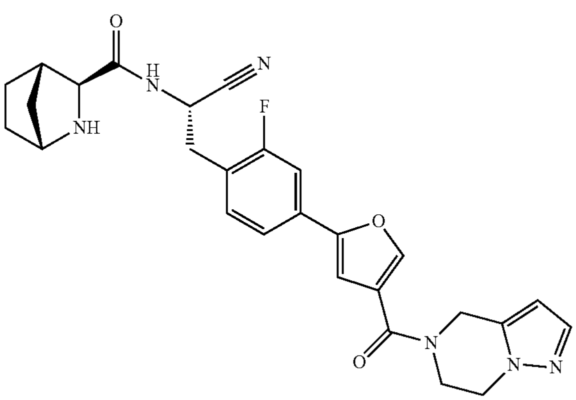
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
238		I-4.3.58	A1/FA	42
239		I-4.3.59	A1/FA	53
240		I-4.3.60	A1/FA	33

TABLE 62-continued

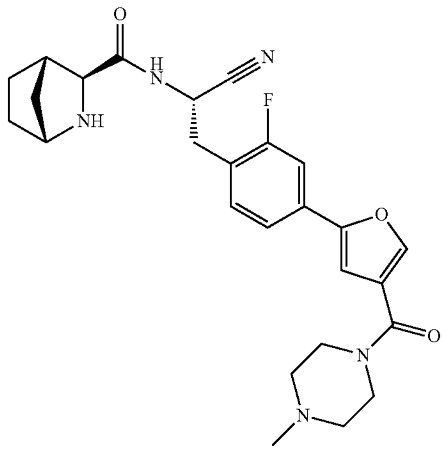
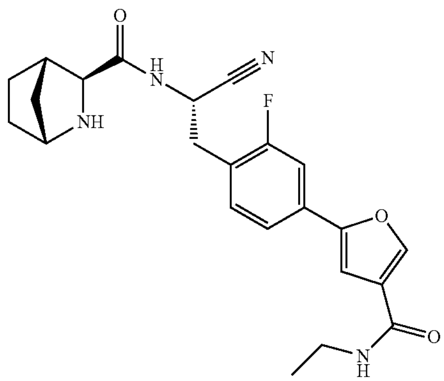
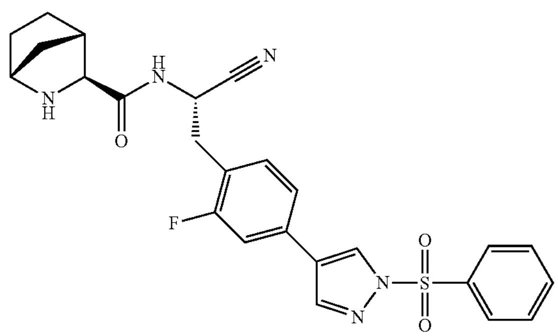
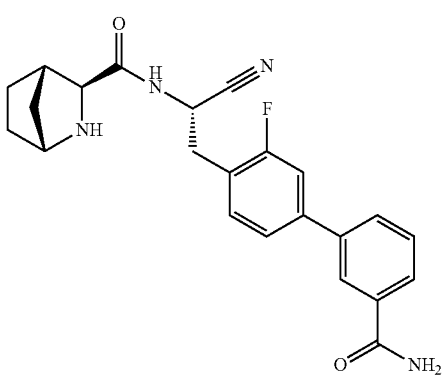
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
241		I-4.3.61	A1/FA	41
242		I-4.3.62	A1/FA	52
243		I-2.3.7.11	A1/FA	62
244		I-4.3.63	A1/FA	43

TABLE 62-continued

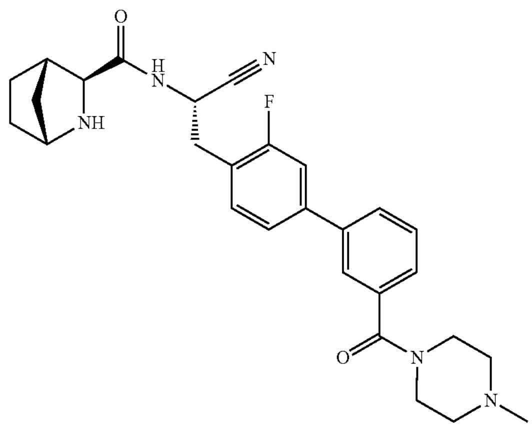
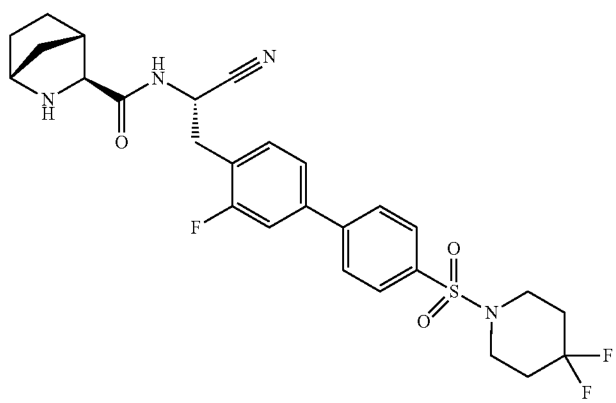
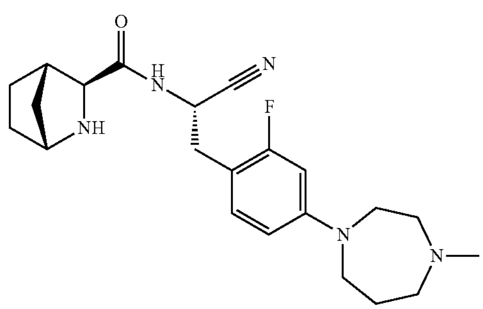
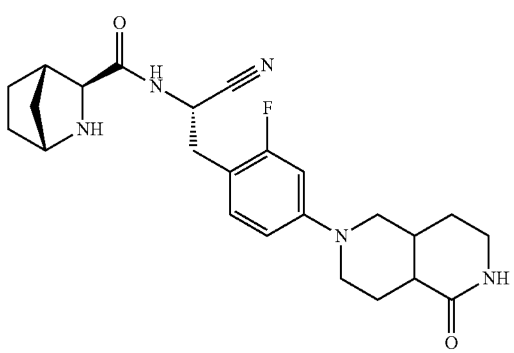
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
245		I-4.3.64	A1/FA	42
246		I-3.2.54	A2.1/SI	63
247		I-3.2.92	A2.2/TSA	20
248		I-3.2.93	A2.2/TSA	78

TABLE 62-continued

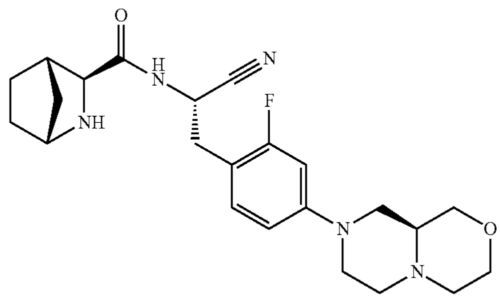
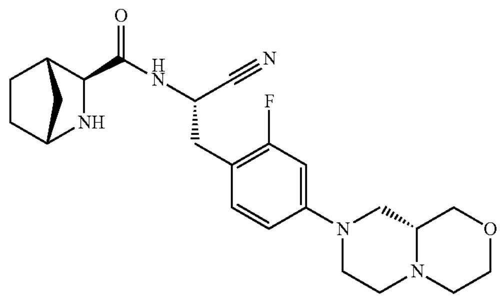
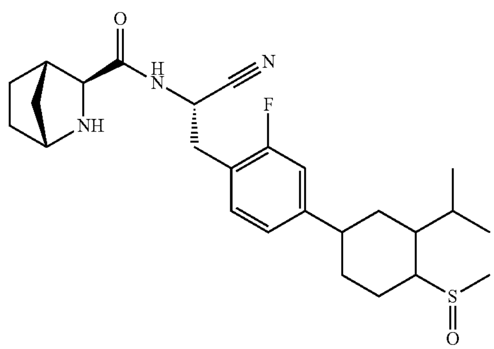
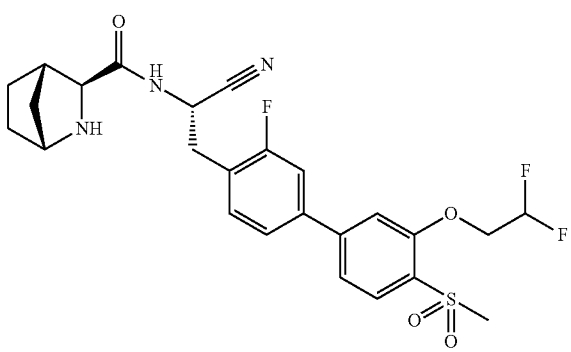
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
249		I-3.2.7	A2.2/TSA	6
250		I-3.2.7	A2.2/TSA	7
251		I-3.2.55	A2.1/TSA	65
252		I-3.2.56	A2.1/TSA	82

TABLE 62-continued

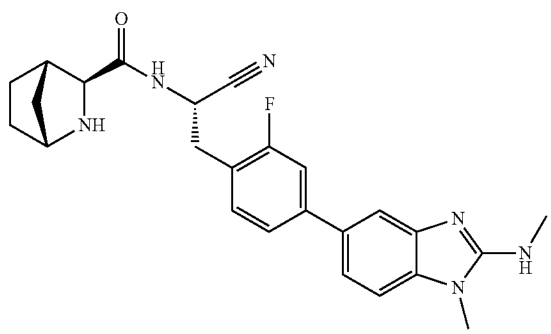
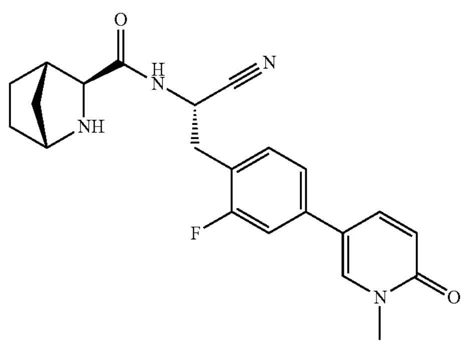
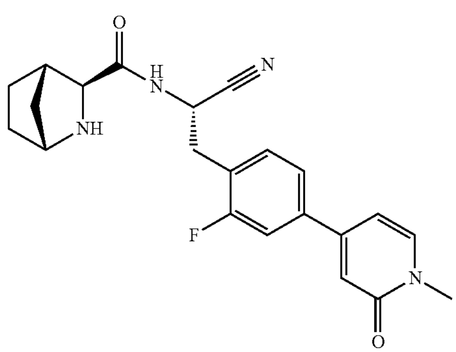
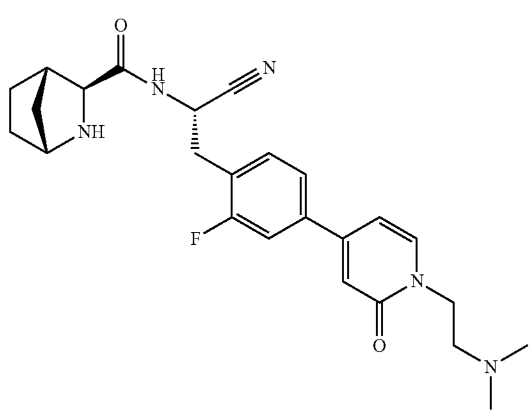
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
253		I-3.2.57	A2.1/TSA	73
254		I-3.2.58	A2.1/TSA	53
255		I-3.2.59	A2.1/TSA	58
256		I-3.2.60	A2.1/TSA	52

TABLE 62-continued

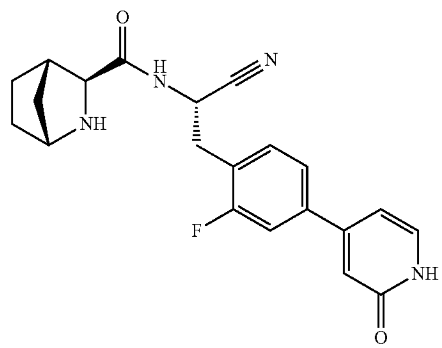
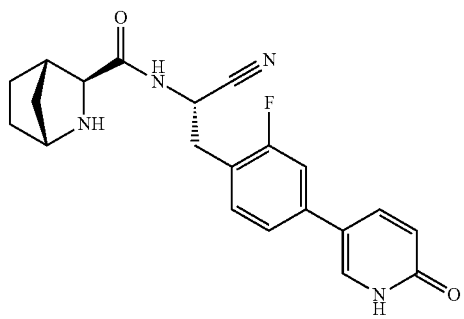
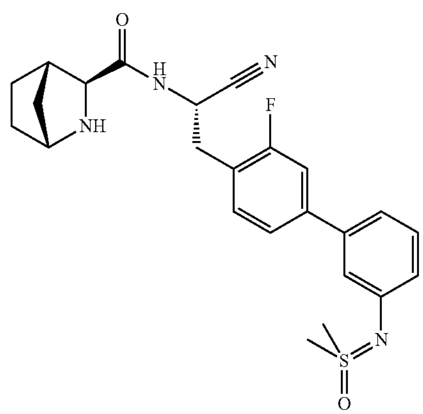
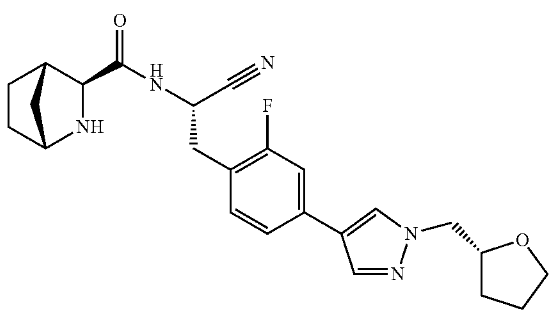
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
257		I-3.2.61	A2.1/TSA	41
258		I-3.2.62	A2.1/TSA	19
259		I-3.2.63	A2.1/FA	19
260		I-3.2.64.1	A2.1/FA	91

TABLE 62-continued

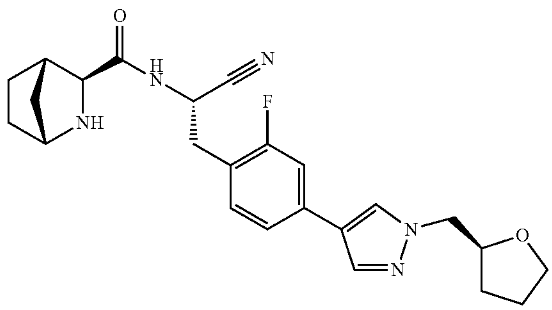
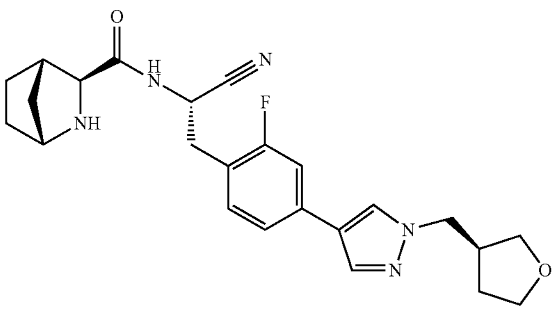
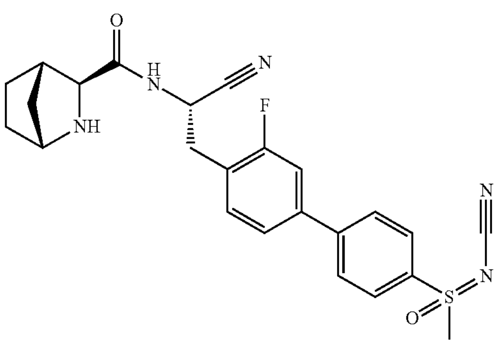
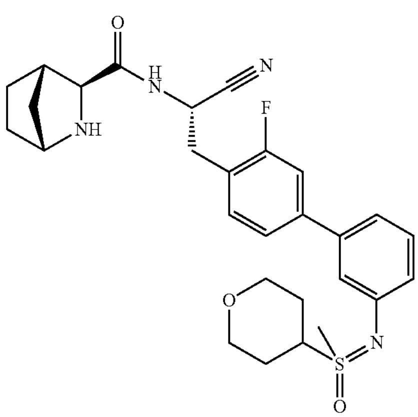
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
261		I-3.2.64.2	A2.1/FA	79
262		I-2.3.7.4.1	A1/FA	53
263		I-3.2.65	A2.1/FA	52
264		I-3.2.66	A2.1/FA	23

TABLE 62-continued

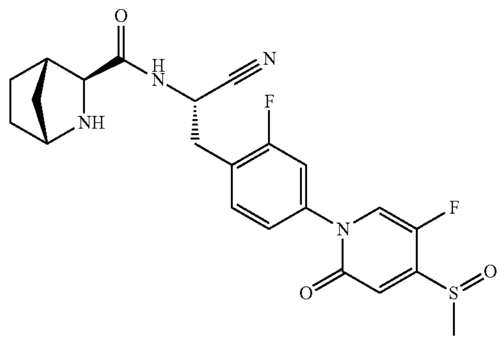
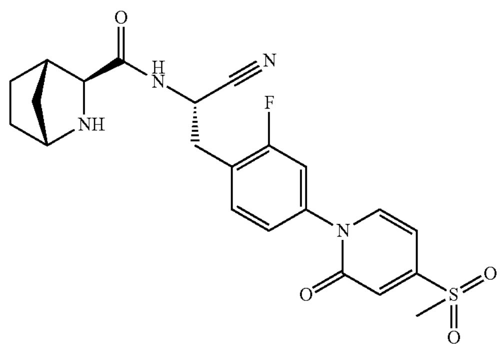
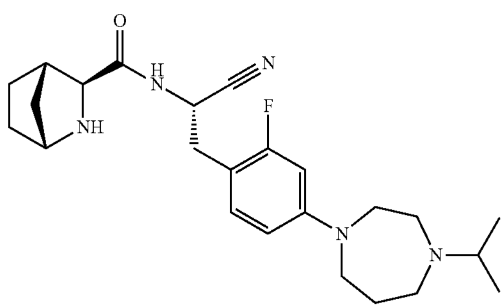
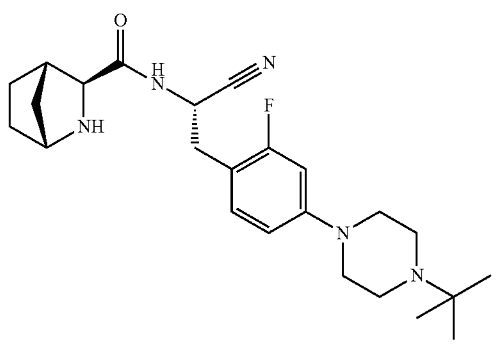
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
265		I-3.2.94	A2.2/TSA	14
266		I-3.2.95	A2.2/TSA	8
267		I-3.2.96	A2.2/TSA	41
268		I-3.2.97	A2.2/TSA	80

TABLE 62-continued

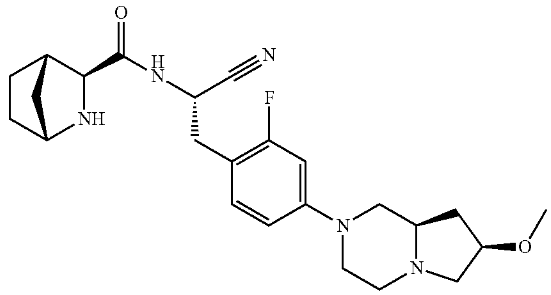
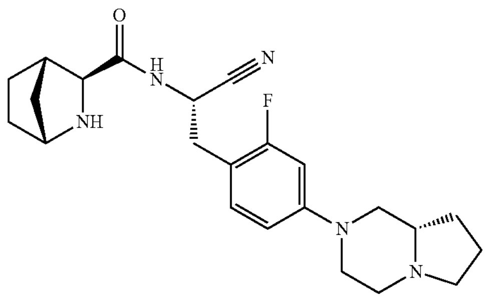
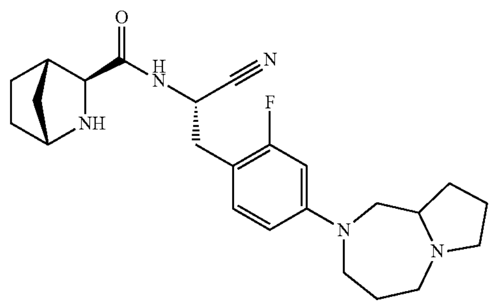
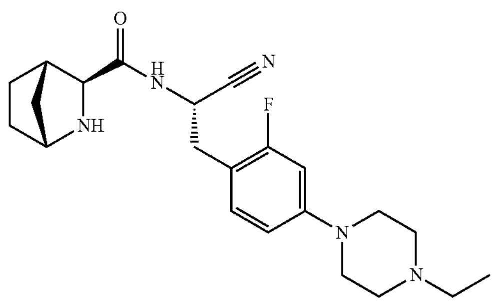
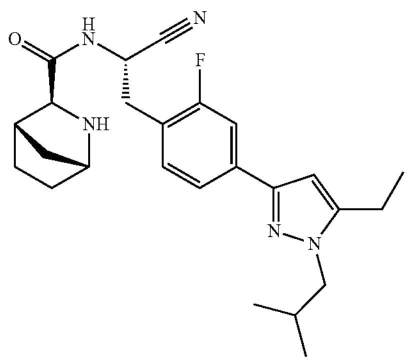
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
269		I-3.2.98	A2.2/TSA	27
270		I-3.2.99	A2.2/TSA	81
271		I-3.2.100	A2.2/TSA	17
272		I-3.2.101	A2.2/TSA	27
273		I-3.2.67	A2.1/TSA	7

TABLE 62-continued

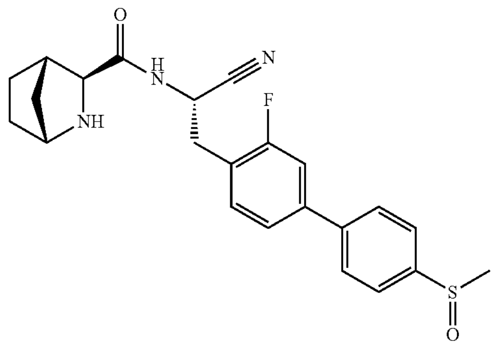
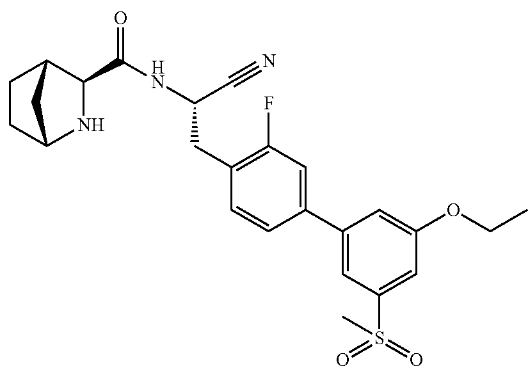
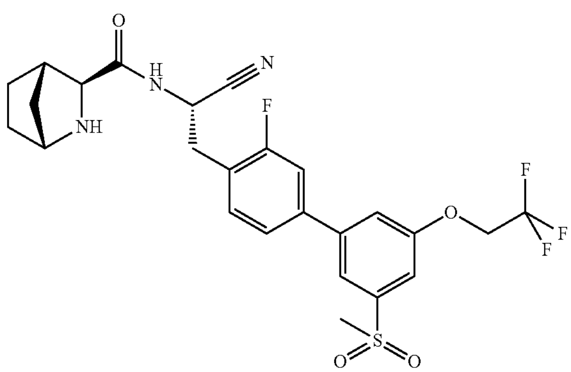
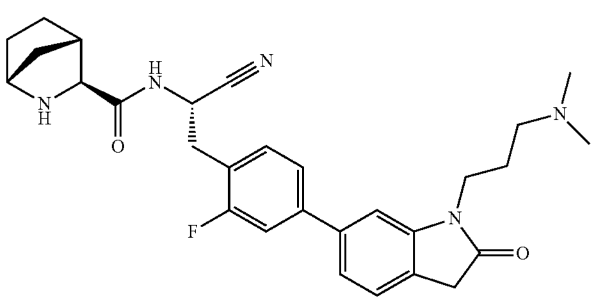
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
274		I-3.2.68	A2.1/TSA	73
275		I-3.2.69	A2.1/TSA	71
276		I-3.2.70	A2.1/TSA	72
277		I-3.2.71	A2.1/TSA	2

TABLE 62-continued

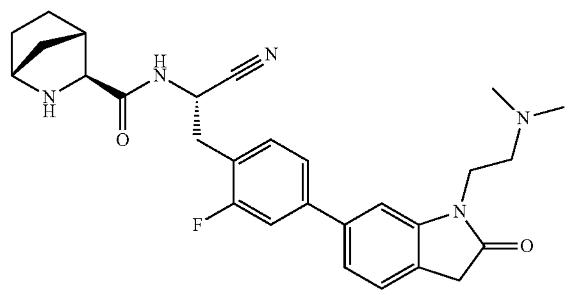
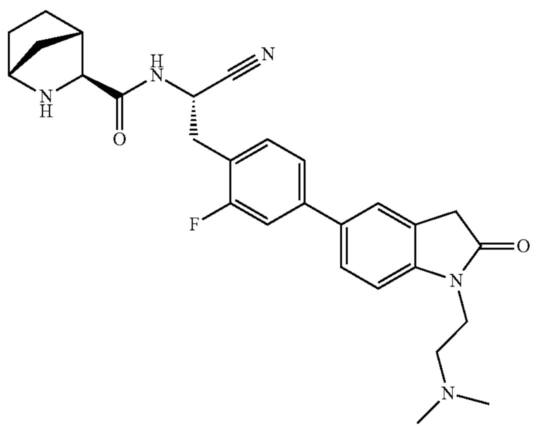
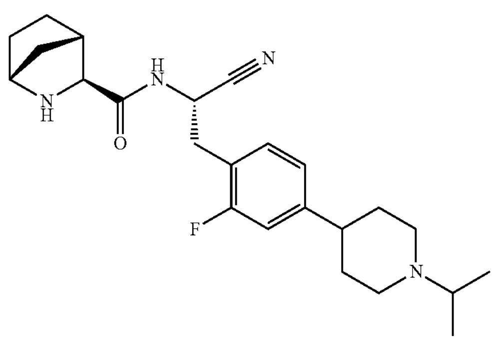
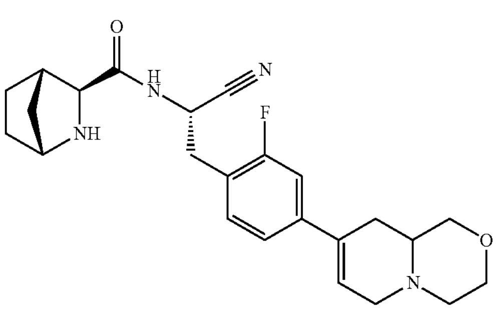
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
278		I-3.2.72	A2.1/TSA	13
279		I-3.2.73	A2.1/TSA	28
280		I-3.3.8	A2.1/SI	90
281		I-3.3.9	A2.1/TSA	83

TABLE 62-continued

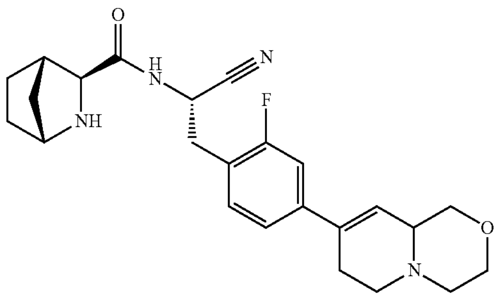
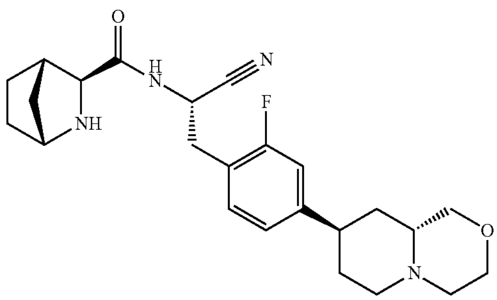
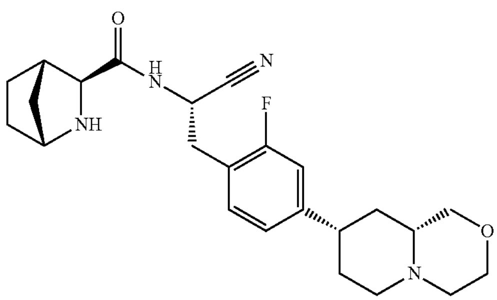
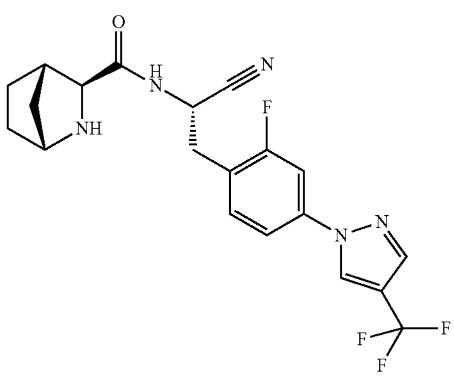
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
282		I-3.3.10	A2.1/TSA	42
283		I-3.3.11	A2.1/TSA	91
284		I-3.3.12	A2.1/TSA	80
285		I-3.2.117	A2.2/TSA	81

TABLE 62-continued

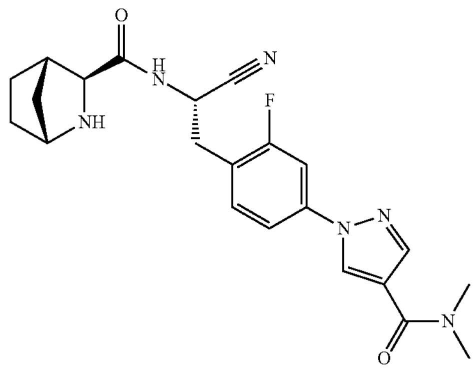
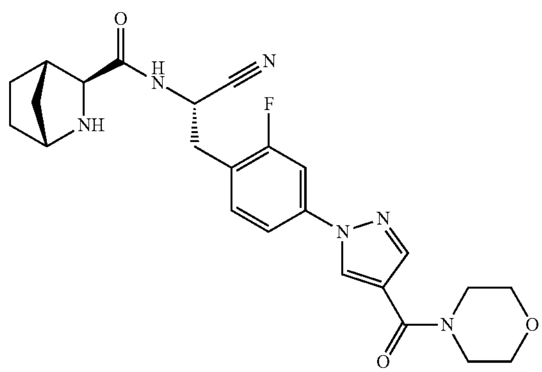
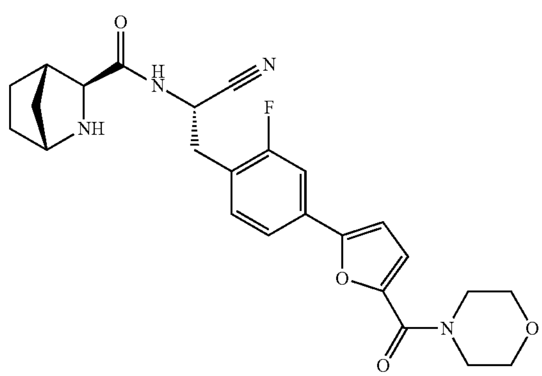
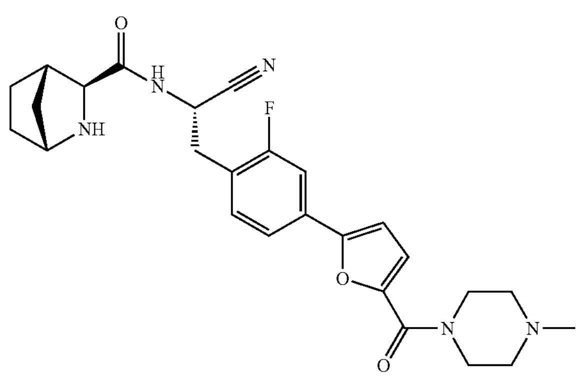
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
286		I-3.2.120	A2.2/TSA	80
287		I-3.2.121	A2.2/TSA	77
288		I-4.3.65	A3/FA	68
289		I-4.3.66	A3/FA	66

TABLE 62-continued

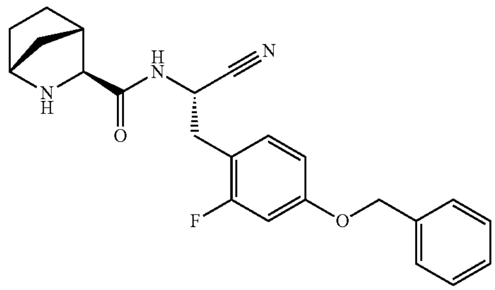
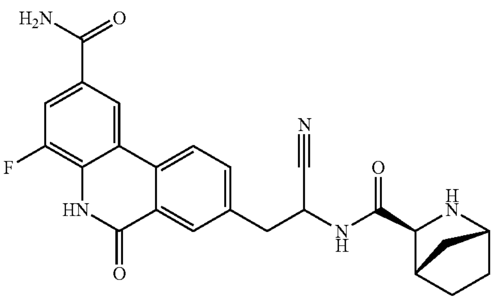
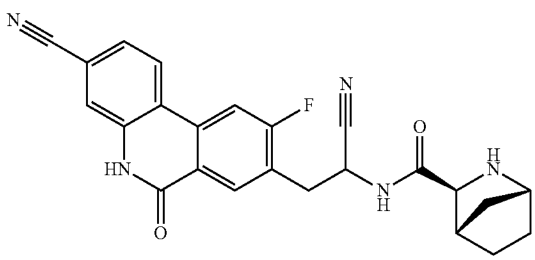
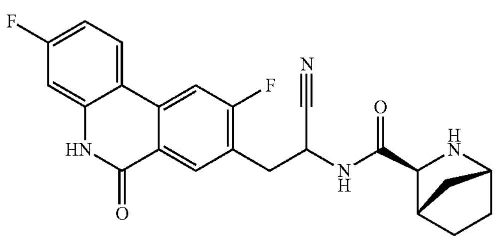
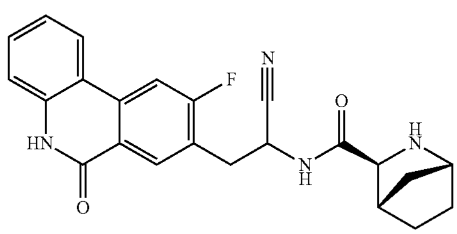
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
290		I-8.2.3	C/TSA	93
291		I-18.2.3	D1/MSA	18
292		I-18.2.1	D1/SI	11
293		I-18.2.2	D1/SI	24
294		I-18.2.4	D1/SI	20

TABLE 62-continued

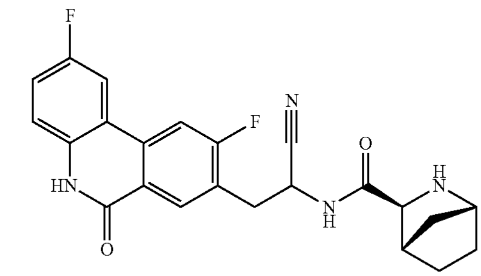
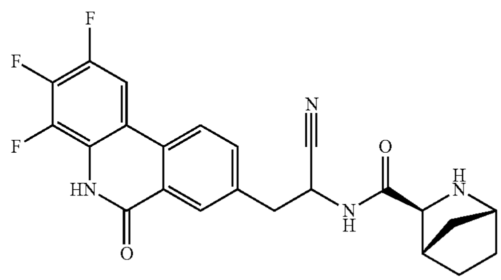
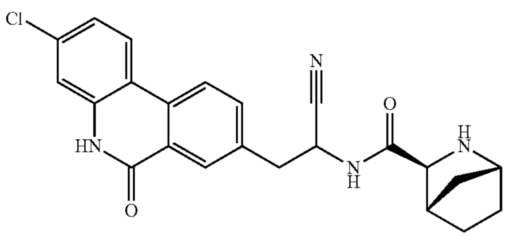
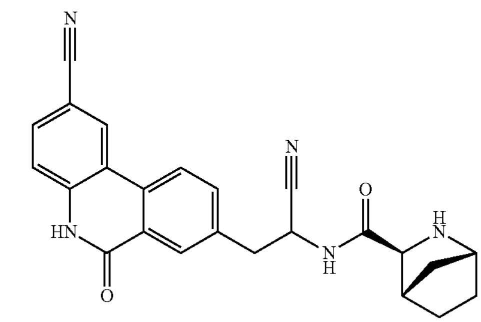
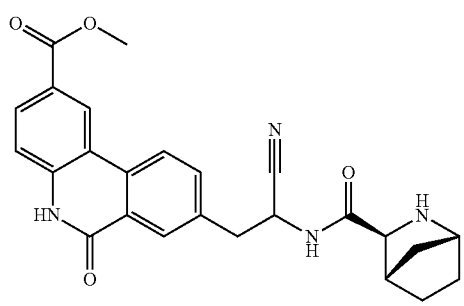
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
295		I-18.2.5	D1/SI	13
296		I-18.2.6	D1/TSA	7
297		I-18.2.7	D1/SI	43
298		I-18.2.8	D1/SI	71
299		I-18.2.9	D1/SI	55

TABLE 62-continued

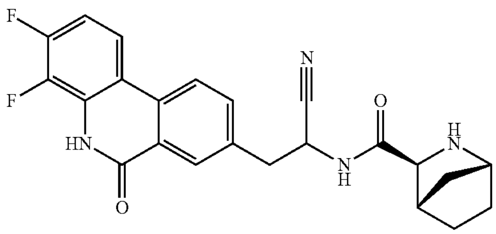
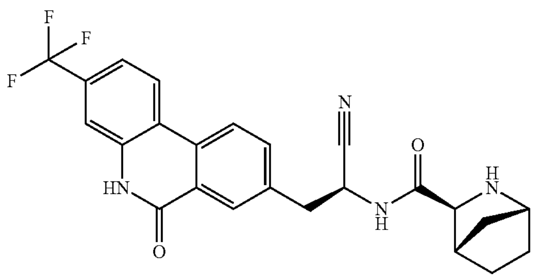
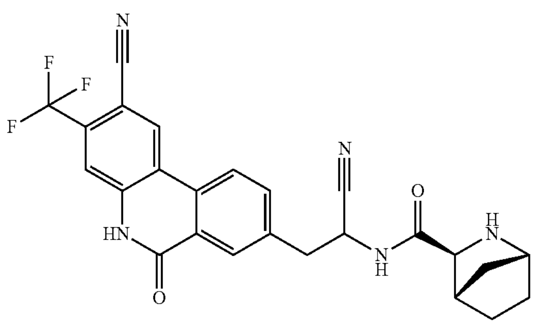
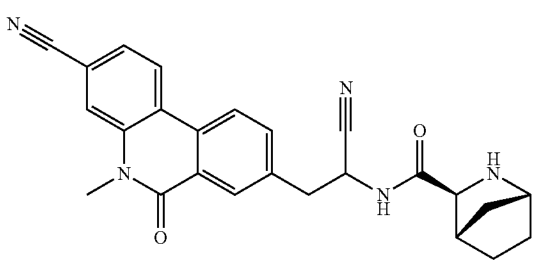
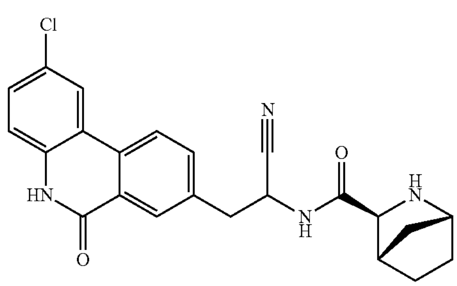
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
300		I-18.2.10	D1/TSA	24
301		I-18.2.11	D1/SI	27
302		I-18.2.12	D1/SI	58
303		I-18.2.13	D1/TSA	29
304		I-18.2.14	D1/SI	32

TABLE 62-continued

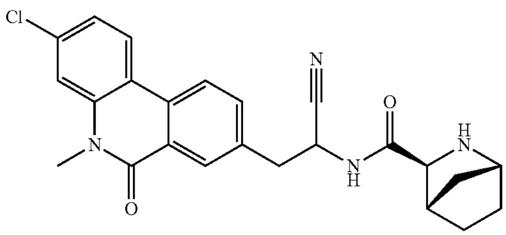
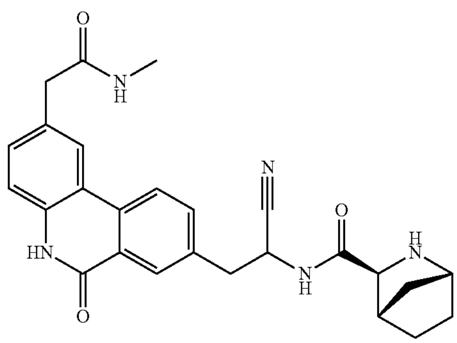
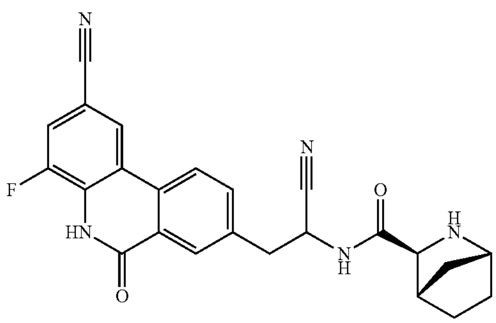
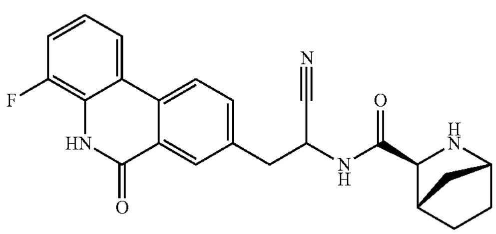
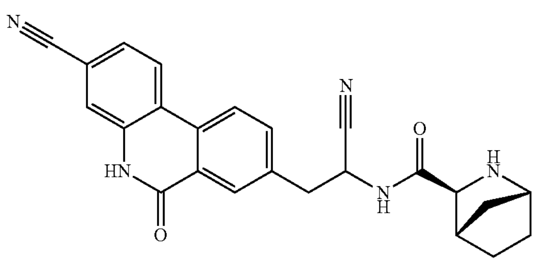
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
305		I-18.2	D1/MSA	14
306		I-18.2.15	D1/MSA	29
307		I-18.2.16	D1/SI	36
308		I-18.2.17	D1/SI	37
309		I-18.2.18	D1/MSA	11

TABLE 62-continued

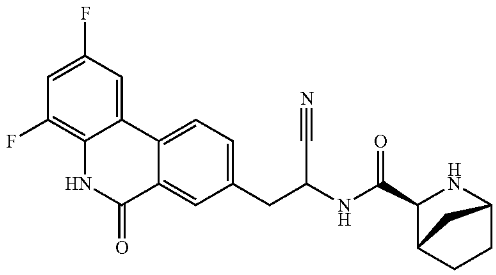
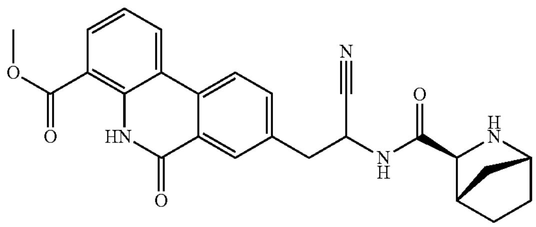
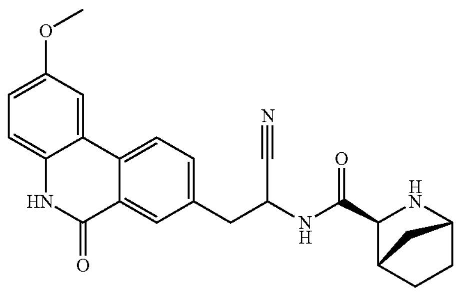
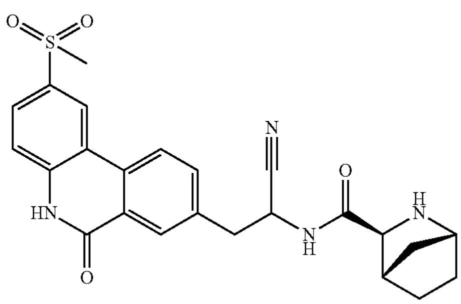
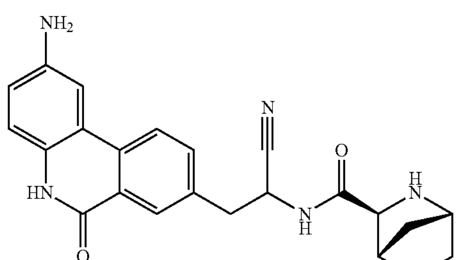
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
310		I-18.2.19	D1/SI	63
311		I-18.2.20	D1/SI	13
312		I-18.2.21	D1/SI	28
313		I-18.2.22	D1/SI	7
314		I-18.2.23	D1/MSA	25

TABLE 62-continued

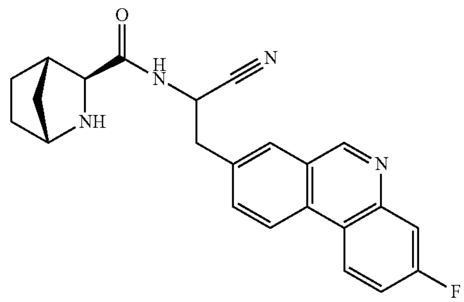
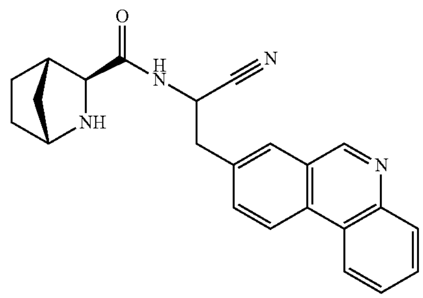
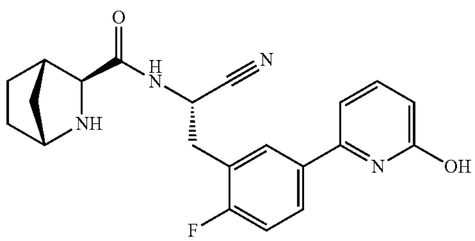
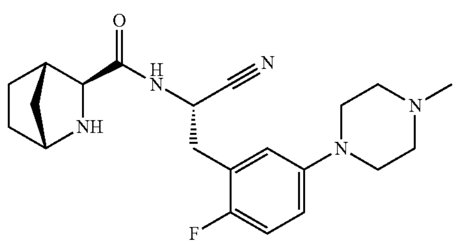
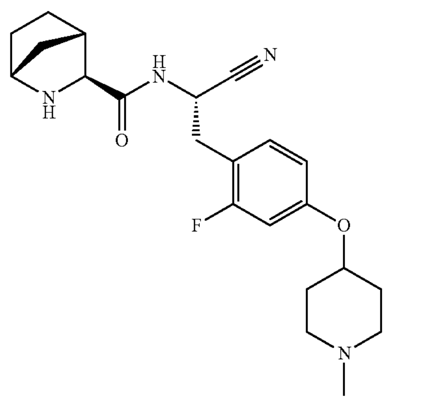
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
315		I-21.3	Z/TSA	60
316		I-21.3.1	Z/TSA	51
317		I-3.2.77	A2.1/TSA	47
318		I-3.2.102	A2.2/TSA	83
319		I-19.1	W/SI	34

TABLE 62-continued

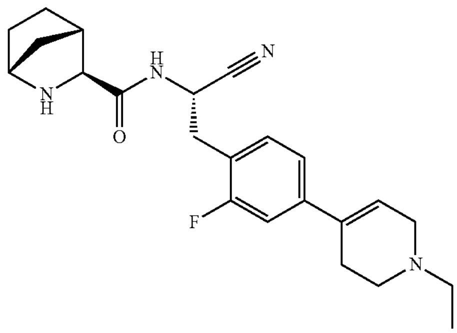
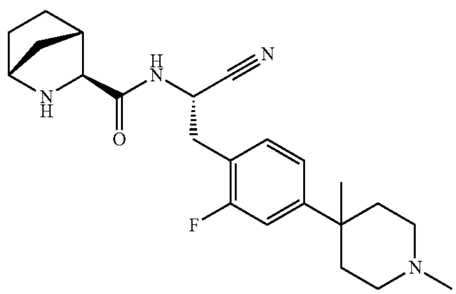
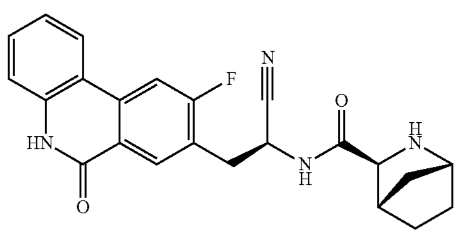
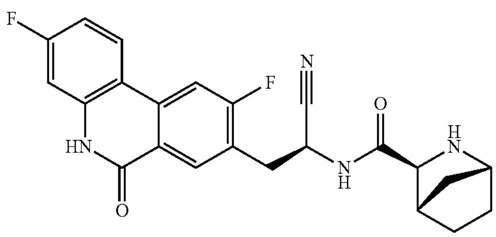
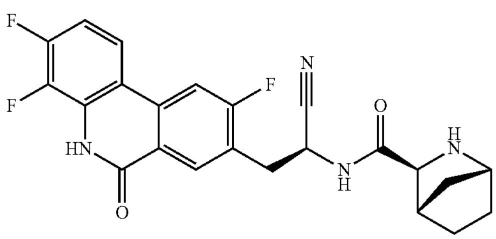
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
320		I-3.3.13	A2.1/SI	74
321		I-8.2.4	C/TSA	91
322		I-18.2.24	D1/TSA	30
323		I-18.2.25	D1/TSA	32
324		I-18.2.26	D1/TSA	36

TABLE 62-continued

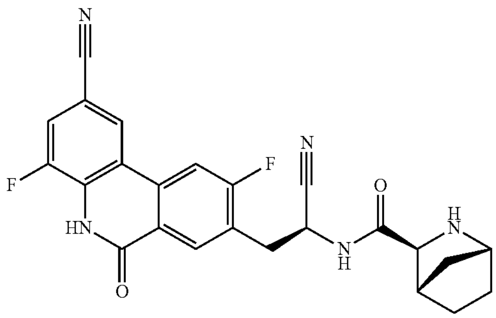
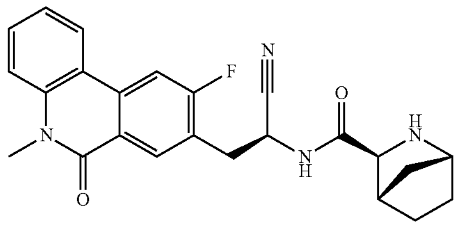
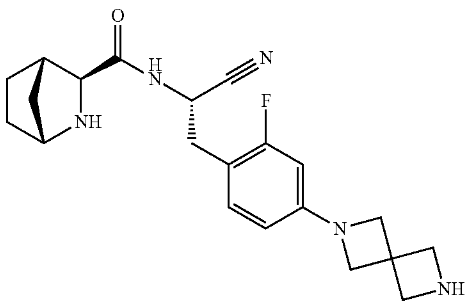
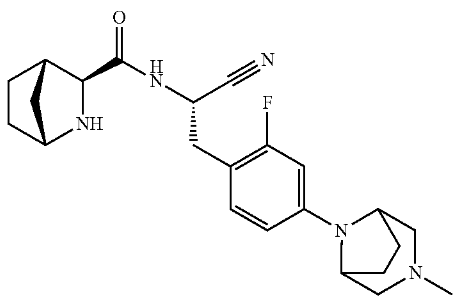
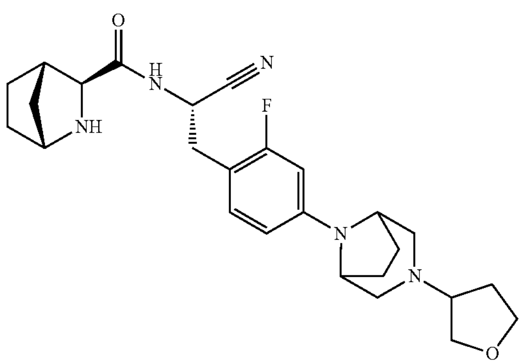
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
325		I-18.2.27	D1/TSA	9
326		I-18.2.28	D1/TSA	30
327		I-3.2.103	A2.2/TSA	62
328		I-3.2.104	A2.2/TSA	86
329		I-3.2.105	A2.2/TSA	62

TABLE 62-continued

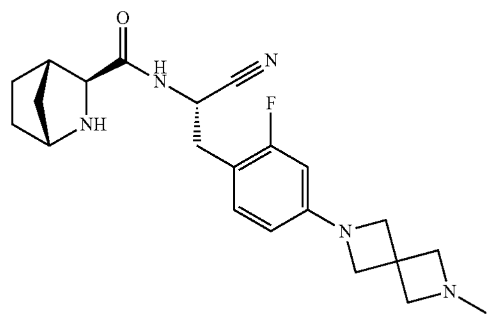
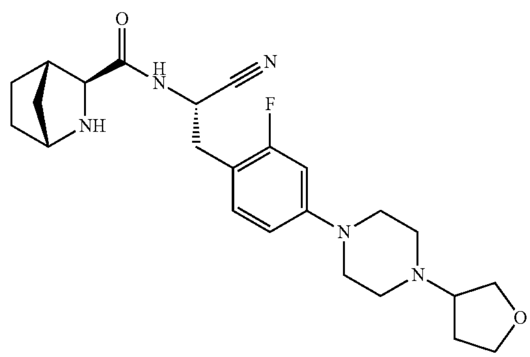
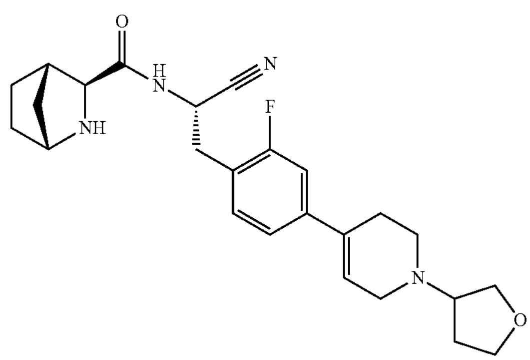
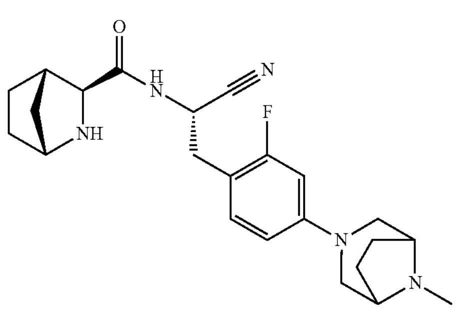
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
330		I-3.2.106	A2.2/TSA	59
331		I-3.2.107	A2.2/TSA	70
332		I-3.2.79	A2.1/TSA	64
333		I-3.2.108	A2.2/TSA	33

TABLE 62-continued

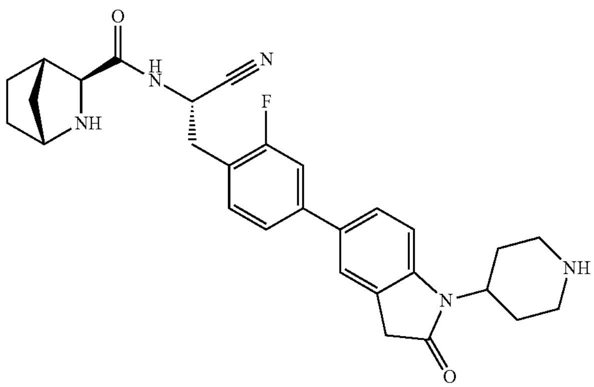
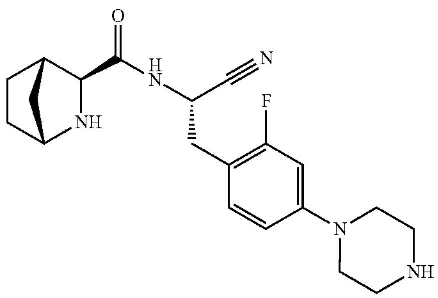
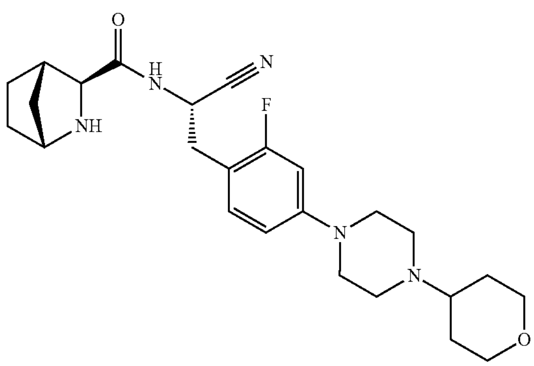
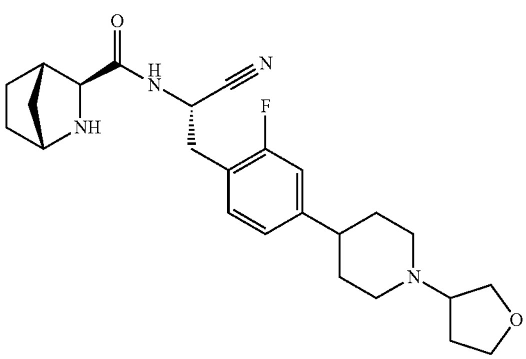
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
334		I-3.2.80	A2.1/TSA	11
335		I-3.2.109	A2.2/TSA	90
336		I-3.2.110	A2.2/TSA	72
337		I-3.3.14	A2.1/TSA	86

TABLE 62-continued

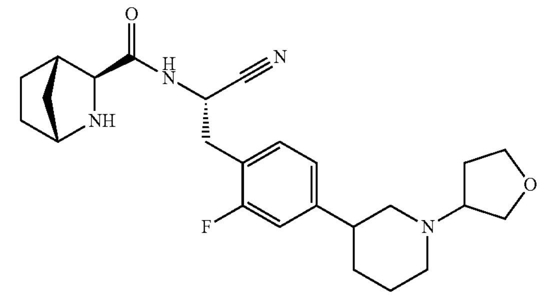
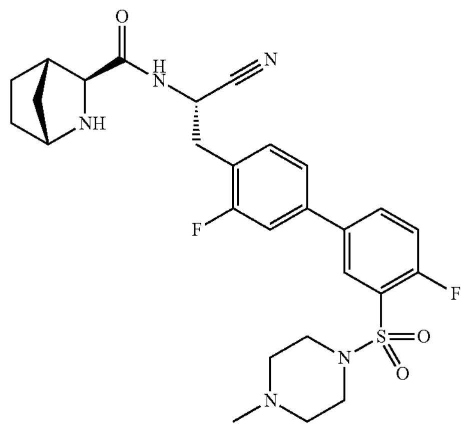
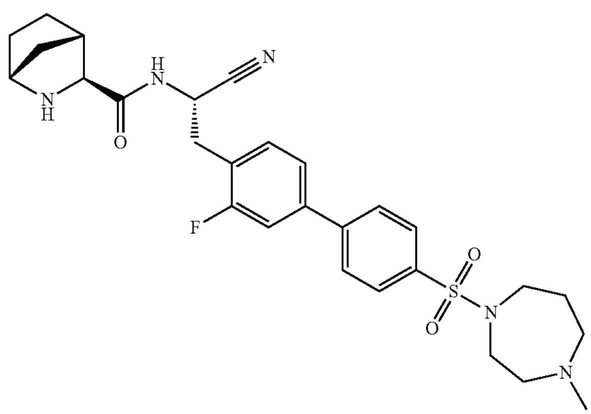
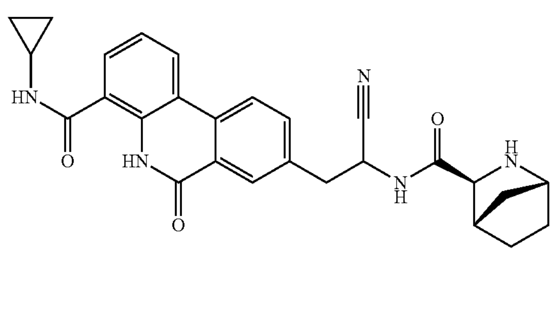
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
338		I-3.3.15	A2.1/TSA	48
339		I-3.2.83	A2.1/TSA	54
340		I-3.2.84	A2.1/TSA	42
341		I-18.2.29	D1/TSA	17

TABLE 62-continued

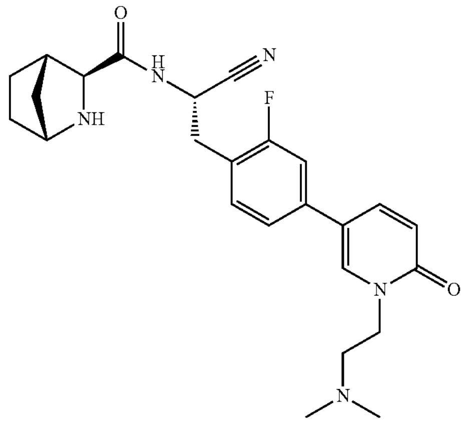
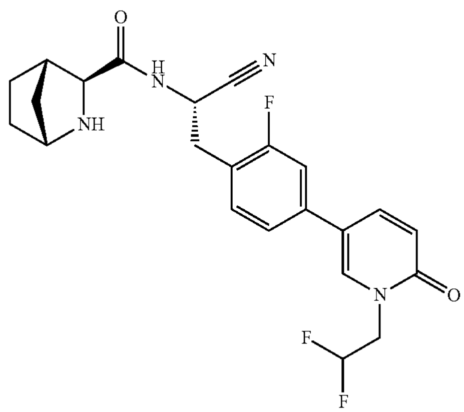
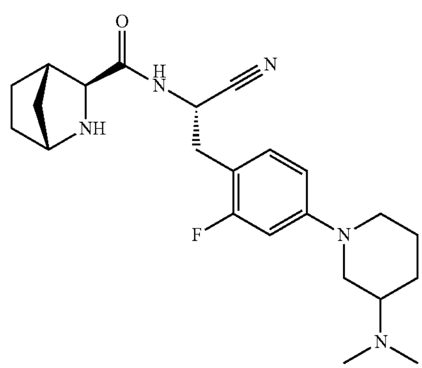
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
342		I-3.2.85	A2.1/TSA	68
343		I-3.2.86	A2.1/TSA	35
344		I-20.1	W1/TSA	28

TABLE 62-continued

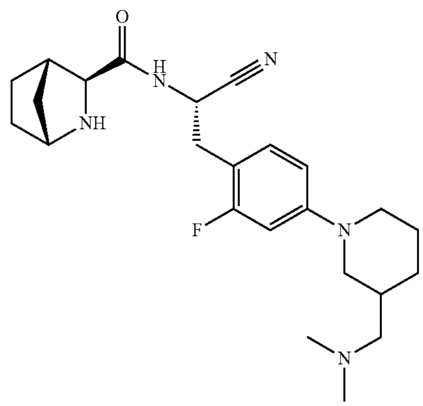
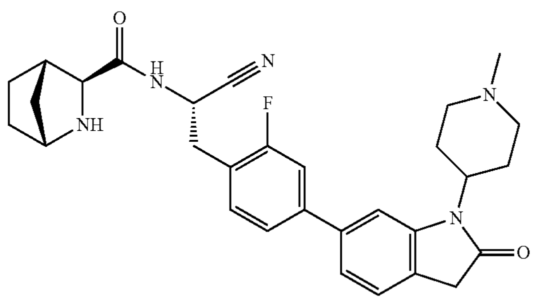
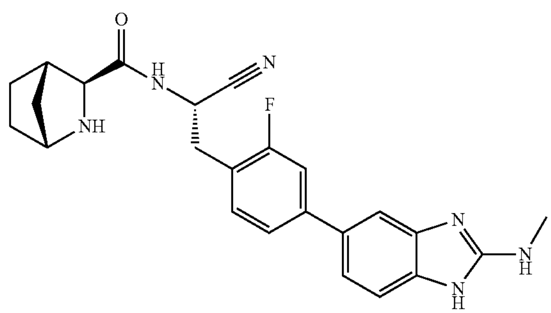
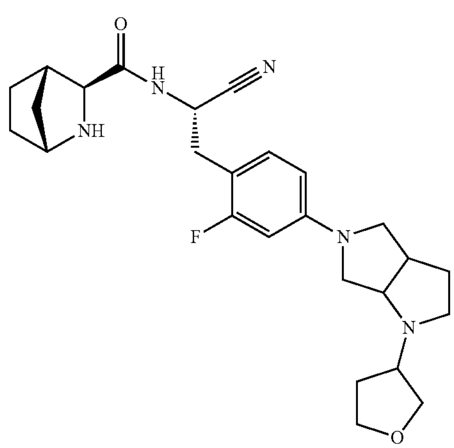
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
345		I-3.2.111	A2.2/TSA	2
346		I-3.2.87	A2.1/TSA	14
347		I-3.2.88	A2.1/TSA	18
348		I-3.3.16	A2.1/TSA	76

TABLE 62-continued

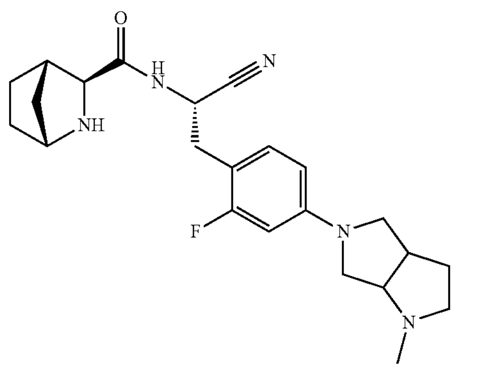
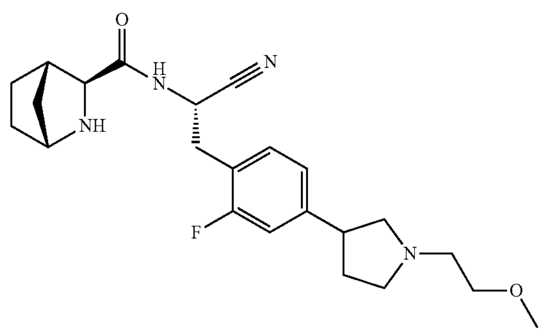
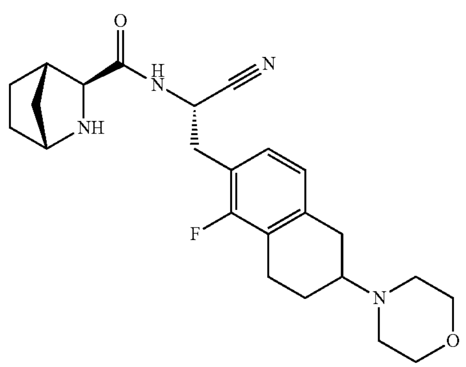
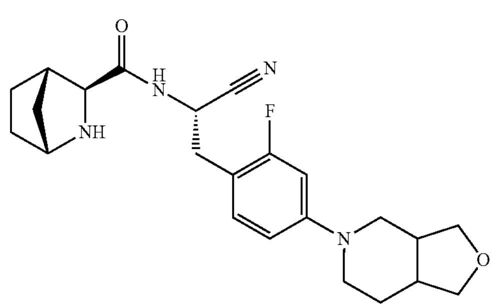
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
349		I-3.3.17	A2.1/TSA	73
350		I-3.3.18	A2.1/TSA	65
351		I-8.2.5	C/TSA	44
352		I-3.2.112	A2.2/TSA	78

TABLE 62-continued

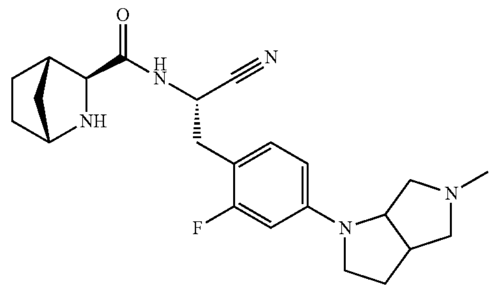
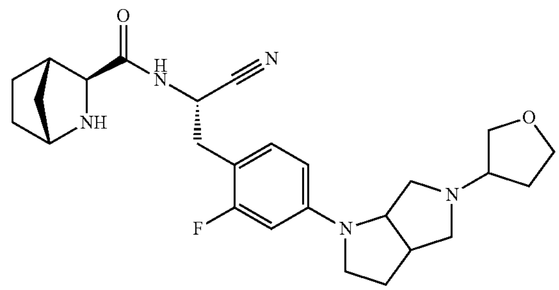
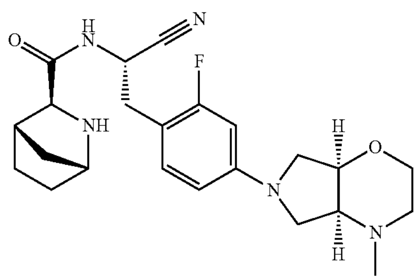
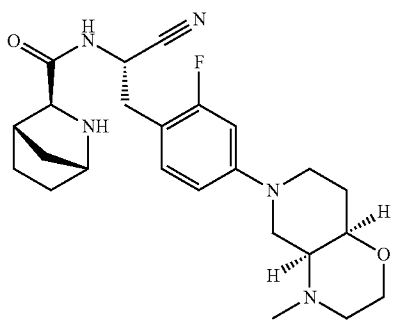
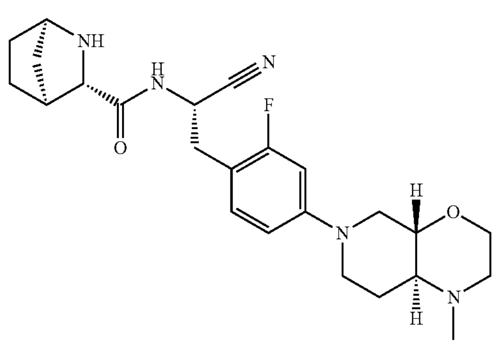
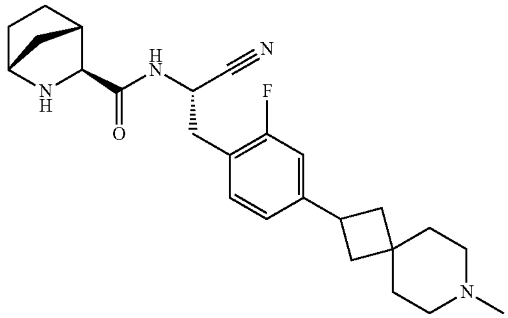
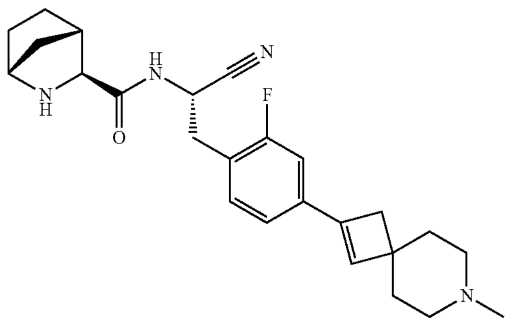
Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
353		I-3.3.19	A2.1/TSA	78
354		I-3.3.20	A2.1/TSA	62
355		I-3.2.114	A2.2/TSA	88
356		I-3.2.115	A2.2/TSA	>95
357		I-3.2.116	A2.2/TSA	80

TABLE 62-continued

Example	Structure	Educt	Syn./ Deprot. Method	Yield [%]
358		Ex 359	A2.1	35
359		I-3.2.136	A2.1/TSA	61

Analytical Data of Examples

TABLE 63

Ex.	m/z [M + H]+	rt [min]	LC-MS-Method
1	419	1.16	V011_S01
2	433	0.59	X011_S01
3	420	0.41	X016_S01
4	442	0.65	Z018_S04
5	470	0.70	Z018_S04
6	386	0.98	V011_S01
7	410	0.96	V018_S01
8	310	0.86	V011_S01
9	387	0.39	X012_S01
10	447	0.42	X012_S01
11	420	0.41	X012_S01
12	460	0.67	Z018_S04
13	426	0.63	Z018_S04
14	467	0.86	V018_S01
15	433	1.04	V001_007
16	442	0.65	Z018_S04
17	428	0.81	004_CA01
18	370	0.80	004_CA01
19	467	0.86	V018_S01
20	396	0.66	Z018_S04
21	438	0.64	Z018_S04
22	419	0.41	Z001_002
23	410	0.78	004_CA01
24	451	0.69	Z018_S04
25	385	0.64	Z018_S04
26	382	0.68	004_CA01
27	368	0.82	004_CA01
28	452	0.70	Z018_S04
29	419	0.41	Z001_002
30	396	0.73	004_CA01
31	451	1.12	V011_S01
32	448	1.28	V011_S01
33	438	0.93	004_CA01

TABLE 63-continued

Ex.	m/z [M + H]+	rt [min]	LC-MS-Method
34	420	1.06	V011_S01
35	407	1.10	V001_007
36	370	0.80	004_CA01
37	443	0.62	Z018_S04
38	439	0.60	004_CA01
39	382	0.64	004_CA01
40	407	0.72	Z018_S04
41	419	0.61	Z018_S04
42	447	1.09	V011_S01
43	428	0.95	V011_S01
44	412	0.63	Z018_S04
45	421	0.90	V012_S01
46	399	0.73	004_CA01
47	461	0.72	Z018_S04
48	438	0.60	X018_S01
49	433	1.13	W018_S01
50	438	0.66	Z018_S04
51	457	0.64	Z018_S04
52	n.d.	n.d.	n.d.
53	407	0.61	Z018_S04
54	442	0.63	Z018_S04
55	493	0.64	Z018_S04
56	443	0.60	Z018_S04
57	452	0.69	004_CA01
58	368	0.79	V018_S01
59	456	0.43	X018_S01
60	418	0.80	004_CA01
61	451	0.88	V018_S01
62	457	0.64	Z018_S04
63	382	0.64	004_CA01
64	410	0.78	004_CA01
65	382	0.64	004_CA05
66	463	0.79	Z011_S03
67	395	0.82	Z011_S03
68	396	0.73	004_CA01
69	354	0.54	004_CA01
70	430	0.72	Z018_S04

TABLE 63-continued

Ex.	m/z [M + H]+	rt [min]	LC-MS-Method
71	456	0.67	Z018_S04
72	412	0.76	004_CA01
73	354	0.70	Z018_S04
74	466	0.70	Z018_S04
75	364	0.50	X012_S01
76	433	0.65	Z018_S04
77	491	0.86	Z011_S03
78	430	0.85	004_CA01
79	419	0.62	Z018_S04
80	399	0.62	004_CA01
81	449	0.90	V012_S01
82	441	0.63	Z018_S04
83	407	1.09	W018_S01
84	471	0.92	Z011_S03
85	395	0.50	X018_S01
86	460	0.67	Z018_S04
87	426	0.66	Z018_S04
88	442	0.64	Z018_S04
89	427	0.75	Z011_S03
90	397	0.60	Z018_S04
91	450	0.98	V011_S01
92	368	0.81	004_CA01
93	397	0.65	Z018_S04
94	461	0.90	Z011_S03
95	419	0.82	V012_S01
96	431	0.78	Z018_S04
97	412	0.65	004_CA01
98	400	0.94	V012_S01
99	468	0.73	Z011_S03
100	436	0.82	004_CA01
101	413	0.70	Z011_S03
102	400	0.92	V012_S01
103	354	0.76	004_CA01
104	368	0.79	004_CA05
105	413	0.79	Z011_S03
106	482	0.81	Z011_S03
107	435	1.25	W018_S01
108	400	0.82	V012_S01
109	441	0.80	Z011_S03
110	382	0.67	004_CA01
111	399	0.58	Z018_S04
112	443	0.75	Z011_S03
113	411	0.70	Z018_S04
114	354	0.59	Z018_S04
115	414	0.68	004_CA01
116	438	0.68	004_CA01
117	385	0.65	V012_S01
118	436	0.77	004_CA01
119	461	0.93	Z011_S03
120	431	0.81	V018_S01
121	383	0.71	004_CA01
122	521	0.97	V018_S01
123	387	0.38	X012_S01
124	427	0.83	Z011_S03
125	400	0.83	V011_S01
126	382	0.66	004_CA01
127	310	0.92	V011_S01
128	387	0.35	X012_S01
129	447	0.76	004_CA01
130	419	0.64	004_CA01
131	433	0.71	004_CA01
132	419	0.84	004_CA01
133	440	0.83	004_CA01
134	431	0.67	004_CA01
135	430	0.74	004_CA01
136	455	0.67	004_CA01
137	430	0.78	004_CA01
138	394	0.70	004_CA01
139	469	0.74	004_CA01
140	469	0.73	004_CA01
141	454	0.72	004_CA01
142	402	0.73	004_CA01
143	455	0.68	004_CA01
144	454	0.73	004_CA01
145	411	0.78	004_CA01
146	419	0.66	004_CA01
147	431	0.64	004_CA01
148	445	0.68	004_CA01
149	445	0.69	004_CA01
150	469	0.73	004_CA01
151	468	0.76	004_CA01
152	460	0.67	Z018_S04
153	468	0.70	Z018_S04
154	456	1.08	V011_S01
155	526	0.80	V012_S01
156	448	0.47	X012_S01
157	413	0.61	Z018_S04
158	477	0.87	V012_S01
159	467	0.85	V018_S01
160	382	0.64	004_CA05
161	427	0.64	Z018_S04
162	379	0.76	004_CA05
163	368	0.61	004_CA05
164	455	0.71	Z018_S04
165	467	0.70	Z018_S04
166	448	0.48	X12_S01
167	397	0.56	004_CA05
168	405	0.66	004_CA05
169	469	1.02	V011_S01
170	441	0.67	Z018_S04
171	430	0.83	004_CA05
172	415	0.87	004_CA05
173	411	0.78	004_CA05
174	405	0.63	004_CA05
175	412	0.74	004_CA05
176	460	0.67	Z18_S04
177	511	1.05	V012_S01
178	444	1.10	V011_S01
179	442	0.86	004_CA05
180	354	0.36	X018_S01
181	437	0.65	Z018_S04
182	430	0.26	X018_S01
183	485	0.67	Z018_S04
184	435	0.67	Z018_S04
185	490	0.55	Z018_S04
186	421	0.63	Z018_S04
187	412	0.26	X018_S01
188	400	1.10	V011_S01
189	416	0.88	V011_S01
190	416	0.89	V011_S01
191	458	1.14	V011_S01
192	400	1.10	V011_S01
193	456	1.00	V011_S01
194	405	0.55	004_CA05
195	399	1.42	V011_S01
196	414	0.65	V018_S01
197	371	1.28	V011_S01
198	442	0.84	004_CA05
199	461	1.24	V012_S01
200	491	0.67	Z018_S04
201	399	0.32	X012_S02
202	477	0.66	Z018_S04
203	359	0.46	X12_S01
204	372	0.93	V011_S01
205	373	1.05	V011_S01
206	401	0.43	X12_S01
207	405	0.41	X12_S01
208	382	0.60	004_CA05
209	372	0.52	X12_S01
210	475	0.74	Z018_S04
211	435	0.67	Z018_S04
212	360	0.48	X12_S01
213	359	0.43	X12_S01
214	467	1.02	V011_S01
215	405	0.37	X12_S01
216	461	0.70	Z018_S04
217	513	0.92	V012_S01
218	470	0.69	Z018_S04
219	461	0.82	V012_S01
220	320	0.39	001_CA07
221	394	0.59	004_CA05
222	466	0.65	Z018_S04
223	383	0.31	X012_S02
224	526	0.36	X012_S01

TABLE 63-continued

Ex.	m/z [M + H]+	rt [min]	LC-MS-Method
225	496	0.54	Z018_S04
226	519	1.17	Z018_S04
227	524	0.56	Z018_S04
228	540	0.83	Z011_S03
229	522	0.9	Z011_S03
230	483	0.8	Z011_S03
231	524	0.77	Z011_S03
232	564	1.31	Z018_S04
233	510	0.76	Z011_S03
234	538	0.95	Z018_S04
235	497	0.82	Z011_S03
236	413	0.60	Z018_S04
237	519	0.68	Z018_S04
238	522	0.66	Z018_S04
239	397	0.37	Z018_S04
240	503	0.64	Z018_S04
241	480	0.53	Z018_S04
242	425	0.64	Z018_S04
243	494	0.74	Z018_S04
244	407	0.73	Z018_S04
245	490	0.56	Z018_S04
246	547	1.05	V012_S01
247	400	0.58	X011_S03
248	440	0.97	V011_S01
249	428	0.97	V011_S01
250	428	0.97	V011_S01
251	468	1.14	V011_S01
252	522	0.61	X011_S02
253	447	0.67	X011_S03
254	395	0.56	004_CA05
255	395	0.55	004_CA05
256	452	0.60	004_CA05
257	381	0.5	004_CA05
258	381	0.50	004_CA05
259	455	0.64	n.d.
260	438	0.66	Z018_S04
261	438	0.65	Z018_S04
262	438	0.65	Z018_S04
263	466	0.65	Z018_S04
264	525	1.19	Z018_S04
265	461	0.59	003_CA04
266	459	0.6	003_CA04
267	428	0.61	004_CA07
268	427	0.59	004_CA07
269	442	0.78	003_CA04
270	412	0.82	003_CA04
271	426	0.65	n.d.
272	400	1.13	V011_S01
273	438	0.73	X011_S03
274	426	0.47	002_CA07
275	486	0.56	002_CA07
276	540	0.58	002_CA07
277	504	0.57	Z020_S01
278	490	0.54	n.d.
279	490	0.53	Z020_S01
280	413	0.35	X012_S02
281	425	1.03	V011_S01
282	425	1.02	V011_S01
283	427	0.49	004_CA07
284	427	0.46	004_CA07
285	422	1.26	V011_S01
286	425	0.58	004_CA05
287	467	0.57	004_CA05
288	467	0.64	Z018_S04
289	480	0.53	Z018_S04
290	394	1.28	V011_S01
291	448	0.64	Z011_S03
292	430	0.51	005_CA01
293	423	0.37	001_CA07
294	405	0.36	001_CA07
295	423	0.37	001_CA07
296	441	0.49	X012_S02_
297	421	0.39	001_CA07
298	412	0.37	X012_S01_
299	445	0.48	002_CA03
300	423	0.41	X012_S01_
301	455	0.47	X012_S01_

TABLE 63-continued

Ex.	m/z [M + H]+	rt [min]	LC-MS-Method
302	480	0.53	002_CA03
303	426	0.47	X012_S02_
304	421	0.51	002_CA03
305	435	0.48	X012_S01_
306	458	0.48	004_CA05
307	430	0.56	004_CA05
308	405	0.35	001_CA07
309	412	0.60	004_CA05
310	423	0.73	003_CA04
311	445	0.52	002_CA03
312	417	0.62	004_CA05
313	465	0.33	X012_S01_
314	402	0.26	X012_S01_
315	389	0.37	X012_S01
316	371	0.31	X012_S01
317	381	0.61	003_CA04
318	386	0.99	V011_S01
319	401	0.31	X012_S02
320	397	0.34	X012_S02
321	399	1.10	V011_S01
322	405	0.75	003_CA04
323	423	0.55	005_CA01
324	441	0.56	005_CA01
325	448	0.53	005_CA01
326	419	0.83	003_CA04
327	384	0.46	002_CA07
328	412	0.74	004_CA05
329	468	0.66	X011_S03
330	398	0.8	003_CA04
331	442	0.72	003_CA04
332	439	0.62	X011_S03
333	412	1.15	V011_S01
334	502	0.54	Z020_S01
335	372	0.93	V011_S01
336	456	0.67	004_CA05
337	441	0.63	X011_S03
338	441	0.29	X018_S02
339	544	0.35	X012_S01
340	540	0.83	003_CA04
341	470	0.40	X012_S01_
342	452	0.47	004_CA07
343	445	0.48	004_CA07
344	414	0.74	004_CA05
345	428	0.30	X012_S01
346	516	0.98	Z011_S03
347	433	0.96	V011_S01
348	468	1.09	V011_S01
349	412	1.14	V011_S01
350	415	0.79	003_CA04
351	427	0.57	X011_S03
352	413	1.11	V011_S01
353	412	0.78	004_CA05
354	468	0.81	003_CA04
355	428	0.90	Z011_S03
356	442	0.91	Z011_S03
357	442	0.93	Z011_S03
358	425	0.71	Z012_S04
359	423	1.06	Z011_S03

Examples representing mixtures of stereoisomers can be detected and resolved into single stereoisomers through analytical and preparative chiral chromatography. Representatives of examples for this process are given in Table 64

TABLE 64

The abbreviation "Dist. example" refers to the distomer of the given example.						
	Analytical SFC Data					Prep.
Example	Methode	Stereoisomer 1 (Exampl No.).	rt [min]	Stereoisomer 2 (Example No.)	rt [min]	SFC Method
15	I_ASH_30_10MIN_SS4P.M	2	3.94	Dist.-2	5.67	chiral SFC E
22	I_ADH_40_MEOH_DEA.M	29	3.60	Dist.-29	5.76	chiral SFC D
43	I_ADH_15_MEOH_DEA.M	249	7.43	250	8.72	chiral SFC C

TABLE 65

List of Abbreviations	
ACN	acetonitrile
AIBN	2,2'-azobis(isobutyronitrile)
ALOX	aluminium oxide
aq.	aqueous
BOC	tert. butyloxycyrbonyle-
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichlormethane
DEA	diethylamine
DIPEA	n,n-diisopropylethylamine
DIPE	diisopropyl ether
DMAP	4-dimethylaminopyridine
DMF	n,n-dimethylformamide
DMSO	dimethyl sulfoxide
EA	ethyl acetate
FA	formic acid
h	hour
HATU	o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate
LiOH	lithium hydroxide
MeOH	methanol
MSA	methanesulfonic acid
MeTHF	methyl tetrahydrofuran
NaH	sodium hydride
PE	petrol ether
RT, r.t.	room temperature, e.g. 15-25° C.
rt	retention time
SI	trimethylsilyl iodide
TBME	tert-butyl methyl ether
TBTU	o-(1H-benzo-1,2,3-triazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TSA	toluene sulfonic acid

PHARMACOLOGICAL DATA

Other features and advantages of the present invention will become apparent from the following more detailed examples which illustrate, by way of example, the principles of the invention.

Inhibition of Human DPPI (Cathepsin C)

Materials: Microtiterplates (Optiplate-384 F) were purchased from PerkinElmer (Prod. No. 6007270). The substrate Gly-Arg-AMC was from Biotrend (Prod.-No. 808756 Custom peptide). Bovine serum albumin (BSA; Prod. No. A3059) and Dithiothreitol (DTT; Prod. No D0632) were from Sigma. TagZyme buffer was from Riedel-de-Haen (Prod.-No. 04269), NaCl was from Merck (Prod.-No. 1.06404.1000) and morpholinoethane sulfonic acid (MES), was from Serva (Prod.-No. 29834). The DPP1 inhibitor Gly-Phe-DMK was purchased from MP Biomedicals (Prod.-No. 03DK00625). The recombinant human DPPI was purchased from Prozymex. All other materials were of highest grade commercially available.

The following buffers were used: MES buffer: 25 mM MES, 50 mM NaCl, 5 mM DTT, adjusted to pH 6.0, containing 0.1% BSA; TAGZyme Buffer: 20 mM NaH_2PO_4, 150 mM NaCl adjusted to pH 6.0 with HCl

Assay Conditions:

The recombinant human DPPI was diluted in TAGZyme buffer to 1 U/ml (38.1 μg/ml, respectively), and then activated by mixing in a 1:2 ratio with a Cysteamine aqueous solution (2 mM) and incubating for 5 min at room temperature.

Five uL test compound (final concentration 0.1 nM to 100 μM) in aqua bidest (containing 4% DMSO, final DMSO concentration 1%) were mixed with 10 μL of DPPI in MES buffer (final concentration 0.0125 ng/μL) and incubated for 10 min. Then, 5 μL of substrate in MES buffer (final concentration 50 μM) were added. The microtiter plates were then incubated at room temperature for 30 min. Then, the reaction was stopped by adding 10 μL of Gly-Phe-DMK in MES-buffer (final concentration 1 μM). The fluorescence in the wells was determined using a Molecular Devices SpectraMax M5 Fluorescence Reader (Ex 360 nm, Em 460 nm) or an Envision Fluorescence Reader (Ex 355 nm, Em 460 nm).

Each assay microtiter plate contained wells with vehicle controls (1% DMSO in bidest+0.075% BSA) as reference for non-inhibited enzyme activity (100% Ctl; high values) and wells with inhibitor (Gly-Phe-DMK, in bidest+1% DMSO+0.075% BSA, final concentration 1 μM) as controls for background fluorescence (0% Ctl; low values).

The analysis of the data was performed by calculating the percentage of fluorescence in the presence of test compound in comparison to the fluorescence of the vehicle control after subtracting the background fluorescence using the following formula:

$$(RFU(\text{sample})-RFU(\text{background}))*100/(RFU(\text{control})-RFU(\text{background}))$$

Data from these calculations were used to generate IC_{50} values for inhibition of DPPI, respectively.

TABLE 66

Example	Inhibition of DPPI IC50 [μM]
1	0.0086
2	0.0020
3	0.0007
4	0.0014
5	0.0040
6	0.0107
7	0.0019
8	0.6794
9	0.0096

TABLE 66-continued

Example	Inhibition of DPPI IC50 [μM]
10	0.0015
11	0.0017
12	0.0019
13	0.0019
14	0.0020
15	0.0020
16	0.0026
17	0.0026
18	0.0027
19	0.0028
20	0.0031
21	0.0031
22	0.0033
23	0.0037
24	0.0037
25	0.0039
26	0.0040
27	0.0040
28	0.0041
29	0.0042
30	0.0042
31	0.0043
32	0.0045
33	0.0045
34	0.0046
35	0.0046
36	0.0047
37	0.0047
38	0.0048
39	0.0051
40	0.0051
41	0.0053
42	0.0053
43	0.0056
44	0.0059
45	0.0063
46	0.0069
47	0.0072
48	0.0072
49	0.0073
50	0.0074
51	0.0075
52	0.0076
53	0.0079
54	0.0082
55	0.0082
56	0.0083
57	0.0083
58	0.0084
59	0.0085
60	0.0087
61	0.0087
62	0.0091
63	0.0093
64	0.0093
65	0.0094
66	0.0094
67	0.0096
68	0.0097
69	0.0099
70	0.0102
71	0.0108
72	0.0108
73	0.0112
74	0.0114
75	0.0114
76	0.0117
77	0.0119
78	0.0120
79	0.0120
80	0.0124
81	0.0131
82	0.0131
83	0.0133
84	0.0137
85	0.0140
86	0.0141
87	0.0142

TABLE 66-continued

Example	Inhibition of DPPI IC50 [μM]
88	0.0152
89	0.0156
90	0.0160
91	0.0170
92	0.0177
93	0.0183
94	0.0187
95	0.0192
96	0.0198
97	0.0199
98	0.0203
99	0.0211
100	0.0223
101	0.0239
102	0.0248
103	0.0249
104	0.0249
105	0.0250
106	0.0259
107	0.0259
108	0.0264
109	0.0269
110	0.0286
111	0.0318
112	0.0333
113	0.0364
114	0.0367
115	0.0378
116	0.0391
117	0.0396
118	0.0443
119	0.0512
120	0.0556
121	0.1565
122	0.1817
123	0.1866
124	0.1869
125	0.2060
126	0.2751
127	0.8597
128	2.3930
129	0.0827
130	0.0435
131	0.1387
132	0.0189
133	0.0161
134	0.0178
135	0.2857
136	0.0102
137	0.0597
138	0.0145
139	0.0117
140	0.0215
141	0.0366
142	0.0631
143	0.0067
144	0.0263
145	0.0538
146	0.0305
147	0.0062
148	0.0304
149	0.0387
150	0.0386
151	0.0369
152	0.0021
153	0.0038
154	0.0135
155	0.0008
156	0.0006
157	0.0009
158	0.0015
159	0.0016
160	0.0017
161	0.0019
162	0.002
163	0.0021
164	0.0023
165	0.0027

TABLE 66-continued

Example	Inhibition of DPPI IC50 [μM]
166	0.0033
167	0.0034
168	0.0037
169	0.0041
170	0.0042
171	0.005
172	0.0052
173	0.0055
174	0.0056
175	0.0063
176	0.0066
177	0.0074
178	0.0074
179	0.0075
180	0.0077
181	0.0086
182	0.0088
183	0.0088
184	0.0088
185	0.009
186	0.0096
187	0.0098
188	0.0098
189	0.0104
190	0.0109
191	0.0112
192	0.0113
193	0.0123
194	0.0133
195	0.0147
196	0.0151
197	0.0156
198	0.0158
199	0.016
200	0.0165
201	0.0201
202	0.0229
203	0.0233
204	0.0245
205	0.0259
206	0.0263
207	0.0291
208	0.0298
209	0.0458
210	0.0494
211	0.0611
212	0.2955
213	0.619
214	0.8148
215	0.8819
216	
217	0.0037
218	0.0189
219	0.0374
220	0.253
221	0.0037
222	0.0022
223	0.0059
224	0.0012
225	0.0008
226	0.0009
227	0.0010
228	0.0016
229	0.0017
230	0.0018
231	0.0022
232	0.0022
233	0.0022
234	0.0038
235	0.0047
236	0.0016
237	0.0046
238	0.0143
239	0.0034
240	0.0061
241	0.0068
242	0.0109
243	0.0048

TABLE 66-continued

Example	Inhibition of DPPI IC50 [μM]
244	0.0037
245	0.0059
246	0.0059
247	0.0084
248	0.0180
249	0.0063
250	0.0042
251	0.0115
252	0.0038
253	0.0110
254	0.0020
255	0.0109
256	0.0263
257	0.0399
258	0.0079
259	0.0060
260	0.0035
261	0.0042
262	0.0064
263	0.0118
264	0.0170
265	0.0627
266	0.0437
267	0.0105
268	0.0111
269	0.0094
270	0.0063
271	0.0059
272	0.0068
273	0.0289
274	0.0065
275	0.0330
276	0.0141
277	0.0030
278	0.0010
279	0.0055
280	0.0212
281	0.0033
282	0.0037
283	0.0097
284	0.0138
285	0.0093
286	0.0389
287	0.0397
288	0.0023
289	0.0025
290	0.0206
291	0.0059
292	0.0009
293	0.0013
294	0.0016
295	0.0021
296	0.0029
297	0.0032
298	0.0032
299	0.0032
300	0.0038
301	0.0045
302	0.0047
303	0.0050
304	0.0060
305	0.0069
306	0.0070
307	0.0072
308	0.0083
309	0.0091
310	0.0094
311	0.0099
312	0.0110
313	0.0136
314	0.0140
315	0.0135
316	0.0424
317	0.0520
318	0.2120
319	0.0175
320	0.0096
321	0.0568

TABLE 66-continued

Example	Inhibition of DPPI IC50 [μM]
322	0.0008
323	0.0008
324	0.0010
325	0.0013
326	0.0019
327	0.0034
328	0.0042
329	0.0070
330	0.0078
331	0.0093
332	0.0129
333	0.0153
334	0.0220
335	0.0245
336	0.0245
337	0.0282
338	0.0443
339	0.0013
340	0.0018
341	0.0076
342	0.0013
343	0.0045
344	0.0100
345	0.0184
346	0.0010
347	0.0085
348	0.0176
349	0.0206
350	0.0386
351	0.0828
352	0.0173
353	0.0065
354	0.0068
355	0.0224
356	0.0200
357	0.0338
358	0.0220
359	0.0088
WO09074829; Example 56	0.0441

Determination of Neutrophil Elastase Activity in U937 Cytosolic Lysate Preparation after Incubation with Test Compound

Materials:

Optiplate 384F were purchased from PerkinElmer (Prod. No. #6007270). 24 well Nunclon cell culture plates (No. 142475) and 96 well plates (No. 267245) were from Nunc. Dimethylsulfoxid (DMSO) was from Sigma (Prod. No. D8418). Nonidet-P40 (NP40) was from USBiological (Prod. No. N3500)

Substrate, specific for Neutrophil elastase, was from Bachem (MeOSuc-Ala-Ala-Pro-Val-AMC; Prod. No. I-1270).

Human neutrophil elastase was from Calbiochem (Prod. No. 324681)

Buffers:

Tris-buffer (100 mM Tris; 1M NaCL; pH 7.5)

Tris-buffer+HSA 0.1%; Human Serum Albumin from Calbiochem (Cat#. 126658)

Serine-protease buffer (20 mM Tris; 100 mM NaCL; pH 7.5)+0.1% HSA

Serine protease lysis buffer: 20 mM Tris-HCL; 100 mM NaCl pH 7.5; +0.2% Nonidet-P40;

PBS: phosphate buffered saline, without Ca and Mg, from Gibco

Cell Culture:

U937 from ECACC (Cat. No. 85011440) cultured in suspension at 37° C. and 5% CO2.

Cell density: 0.2-1 Mio. Cells/ml.

Medium: RPMI1640 GlutaMAX (No. 61870) with 10% FCS from Gibco

Cell Seeding and Treatment:

Compounds in 100% DMSO were diluted in Medium (-FCS) with 10% DMSO and further diluted according to the experiment planned.

20 μl of the compound solution was transferred in the respective wells of the 24 well plate and diluted with 2 ml cell suspension/well containing 1,105 cells/ml (final concentration of DMSO=0.1%). Compound dilution factor=100

Compounds (up to 7 concentrations) were tested in triplicates with 3 wells for the DMSO 0.1% control, incubated for 48 hours without medium change at 37° C., 5% CO2 and 95% relative humidity.

Cell Harvesting and Cell Lysate:

Transfer the cell suspension in 2.2 ml Eppendorf cups. Separate cells from medium by centrifugation (400×g; 5 min; RT); discard the supernatant. Resuspend in 1 ml PBS; centrifugation (400×g; 5 min; RT); wash cells twice with PBS. Add 100 μl Serin lysis buffer (ice cold) to the cell pellet; resuspend the pellet and store on ice for 15 minutes. Remove debris by centrifugation at 15000×g for 10 min at 4° C. Transfer 80-100 μl lysate supernatant in 96 well plate and store immediately at −80° C.

Neutrophil Elastase Activity Assay:

Frozen lysates were thawn at 37° C. for 10 minutes and stored on ice. Protein content was determined with Bradford protein assay. Lysates were diluted to 0.2-0.5 mg/ml protein in serine protease buffer+HSA.

Standard: NE (100 g/ml stocksolution in Tris-buffer; stored at −80° C.) was diluted in Tris-buffer+HSA to 750 ng/ml, and further serially diluted 1:2 for the standard curve.

Buffer, blank, standard and lysate samples were transferred into 384 well plate

Pipetting Plan

Blank: 5 μl Tris-buffer+10 μl Tris-buffer+HSA+5 μl Substrate

Standard: 5 μl Tris-buffer+10 μl NE (diff. conc.)+5 μl Substrate

Lysate: 5 μl Tris-buffer+10 μl Lysat+5 μl Substrate

The increase in fluorescence (Ex360 nm/Em 460 nm) is determined over 30 minutes with a Molecular Device Spectramax M5 Fluorescence Reader. Kinetic Reduction (Vmax units/sec); 4 vmax points. The amount of neutrophil elastase (ng/ml) is calculated using the standard curve and the Spectramax software. The result is interpolated to ng/mg lysate protein using excel formula functions. Percent inhibition in the compound-treated lysate samples is calculated relative to the DMSO-treated control-sample (100−(compound-sample*100)/control-sample) A test compound will give values between 0% and 100% inhibition of neutrophil elastase. IC50 is calculated using Graphpad Prism; nonlinear fitting (log(inhibitor) vs. response—Variable slope). The IC50 value is interpolated as the concentration of test compound which leads to a neutrophil elastase activity reduction of 50% (relative to the DMSO-treated control).

TABLE 67

Example	Reduction of NE-activity in U937 cells IC50 [μM]
1	0.0023
2	0.0062
3	0.0029
4	0.0064
6	0.0024
11	0.0087
16	0.0145
29	0.0088

TABLE 67-continued

Example	Reduction of NE-activity in U937 cells IC50 [μM]
42	0.0083
43	0.0092
154	0.0046
155	0.0005
156	0.0023
158	0.0088
169	0.0091
177	0.0092
178	0.0036
182	0.0081
185	0.0039
187	0.0073
188	0.0044
191	0.0033
192	0.0041
193	0.0065
196	0.0053
217	0.0075
223	0.0030
224	0.0010
225	0.0028
226	0.0018
227	0.0009
228	0.0046
229	0.0029
232	0.0052
234	0.0069
237	0.0096
241	0.0053
245	0.0038
247	0.0080
249	0.0165
250	0.0115
253	0.0055
254	0.0305
267	0.0027
268	0.0007
269	0.0055
270	0.0014
271	0.0017
272	0.0024
277	0.0036
278	0.0010
279	0.0019
281	0.0019
282	0.0034
283	0.0045
284	0.0053
289	0.0039
293	0.0046
294	0.0078
295	0.0086
300	0.0089
303	0.0083
319	0.0093
320	0.0037
322	0.0021
323	0.0014
324	0.0013
325	0.0047
326	0.0019
328	0.0012
329	0.0025
330	0.0377
331	0.0060
332	0.0058
333	0.0047
339	0.0006
340	0.0008
342	0.0247
343	0.0169
344	0.0041
345	0.0069
346	0.0068
348	0.0020
349	0.0028

TABLE 67-continued

Example	Reduction of NE-activity in U937 cells IC50 [μM]
358	0.0037
359	0.0029
WO09074829; Example 56	0.1067

Inhibition of Human Cathepsin K

Materials: Microtiterplates (Optiplate-384 F were purchased from PerkinElmer (Prod. No. 6007270). The substrate Z-Gly-Pro-Arg-AMC was from Biomol (Prod.-No. P-142). L-Cysteine (Prod. No. 168149) was from Sigma. Sodium acetate was from Merck (Prod.-No. 6268.0250), EDTA was from Fluka (Prod.-No. 03680). The inhibitor E-64 was purchased from Sigma (Prod.-No. E3132). The recombinant human Cathepsin K proenzyme was purchased from Biomol (Prod. No. SE-367). All other materials were of highest grade commercially available.

The following buffers were used: Activation buffer: 32.5 mM sodium acetate, adjusted to pH 3.5 with HCl; Assay buffer: 150 mM sodium acetate, 4 mM EDTA, 20 mM L-Cysteine, adjusted to pH 5.5 with HCl,

Assay Conditions:

To activate the proenzyme, 5 μl procathepsin K were mixed with 1 ul activation buffer, and incubated at room temperature for 30 min.

5 μL test compound (final concentration 0.1 nM to 100 μM) in aqua bidest (containing 4% DMSO, final DMSO concentration 1%) were mixed with 10 uL of Cathepsin K in assay buffer (final concentration 2 ng/μL) and incubated for 10 min. Then 5 μL of substrate in assay buffer (final concentration 12.5 μM) were added. The plates were then incubated at room temperature for 60 min. Then, the reaction was stopped by adding 10 μL of E64 in assay buffer (final concentration 1 μM). The fluorescence in the wells was determined using a Molecular Devices SpectraMax M5 Fluorescence Reader (Ex 360 nm, Em 460 nm).

Each assay microtiter plate contains wells with vehicle controls (1% DMSO in bidest) as reference for non-inhibited enzyme activity (100% Ctl; high values) and wells with inhibitor (E64 in bidest+1% DMSO, final concentration 1 M) as controls for background fluorescence (0% Ctl; low values). The analysis of the data was performed by calculating the percentage of fluorescence in the presence of test compound in comparison to the fluorescence of the vehicle control after subtracting the background fluorescence:

$$(RFU(\text{sample})-RFU(\text{background}))^* 100/(RFU(\text{control})-RFU(\text{background}))$$

Data from these calculations were used to generate IC_{50} values for inhibition of Cathepsin K, respectively.

TABLE 68

Example	Inhibition of Cathepsin K IC50 [μM]
2	2.8
3	2.1
4	2.6
5	2.6
6	2.5
7	8.0
10	2.7
11	2.6
12	2.1
13	3.4
14	2.7

TABLE 68-continued

Example	Inhibition of Cathepsin K IC50 [μM]
15	3.2
16	2.1
17	6.1
18	3.0
19	5.4
20	2.9
21	4.9
22	3.2
23	3.8
24	13.3
25	6.3
26	3.6
27	3.2
28	2.7
29	1.4
30	3.1
31	7.3
32	3.9
33	4.8
34	2.5
35	4.4
36	3.0
37	5.1
38	2.9
39	7.8
40	7.8
41	4.7
42	2.9
43	2.2
44	4.0
45	4.4
46	4.0
47	3.4
48	3.3
49	6.5
50	3.6
51	4.9
52	17.0
53	4.1
54	4.5
55	3.9
56	4.0
57	2.3
58	11.1
59	2.5
60	12.3
61	10.9
62	3.9
63	6.2
64	4.2
65	11.7
66	4.8
67	4.6
68	7.3
69	2.4
70	12.0
71	4.8
72	7.3
73	3.1
74	2.5
75	5.3
76	5.3
77	5.3
78	6.7
79	3.5
80	4.1
81	4.5
82	5.4
83	5.1
84	4.9
85	3.0
86	6.8
88	8.8
89	5.4
90	3.5
91	2.5
92	8.2

TABLE 68-continued

Example	Inhibition of Cathepsin K IC50 [μM]
93	6.9
94	4.9
95	3.6
96	5.5
97	7.9
98	8.4
99	2.9
100	8.2
101	6.5
102	4.3
103	5.9
104	10.3
105	5.2
106	5.3
107	4.7
108	9.4
109	4.5
110	9.8
111	4.3
112	5.6
113	8.3
114	6.8
115	2.3
116	7.7
117	2.7
118	3.9
119	4.5
121	5.2
130	10.2
132	12.2
133	19.4
134	6.7
136	6.2
138	6.4
139	4.8
140	8.4
141	8.8
143	5.1
144	11.1
145	7.4
146	9.6
147	9.7
148	14.6
149	7.6
150	9.3
151	4.8
152	6.1
153	4.4
154	4.6
155	1.0
156	7.8
157	7.4
158	9.4
159	3.3
161	10.7
167	6.3
169	5.2
176	13.9
181	9.7
182	3.5
185	1.7
186	3.5
190	3.7
193	2.2
199	11.7
200	3.3
201	2.5
203	8.4
218	26.0
222	1.7
228	2.0
229	1.6
230	5.9
231	2.4
233	3.0
234	2.9
235	3.0

TABLE 68-continued

Example	Inhibition of Cathepsin K IC50 [μM]
236	1.7
237	1.9
238	9.3
239	2.0
240	9.4
241	2.5
242	2.5
244	2.0
245	1.2
247	4.5
249	3.6
250	3.1
252	3.3
253	5.7
254	4.5
259	3.7
260	3.9
261	3.8
262	2.8
263	2.1
267	4.7
268	3.8
269	1.7
270	6.1
274	3.5
276	5.5
278	1.2
281	1.9
282	1.8
283	3.6
285	8.7
288	2.2
293	2.7
294	2.2
295	4.7
296	>30.0
297	12.4
298	17.6
300	23.1
301	19.5
303	22.2
315	>30.0
319	4.5
322	1.1
323	0.9
324	0.8
325	2.3
326	1.1
328	7.7
330	6.6
331	1.5
332	6.2
333	2.4
343	5.3
344	6.2
345	9.2
346	4.0
348	4.3
349	5.0
358	9.6
359	6.3
WO09074829; Example 56	0.4

Determination of Metabolic Stability with Human Liver Microsomes

The metabolic degradation of the test compound is assayed at 37° C. with pooled human liver microsomes. The final incubation volume of 100 μl per time point contains TRIS buffer pH 7.6 (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/ml) and the test compound at a final concentration of 1 μM. Following a short preincubation period at 37° C., the reactions are initiated by addition of beta-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM) and terminated by transferring an aliquot into acetonitrile after different time points. Additionally, the NADPH-independent degradation is monitored in incubations without NADPH, terminated at the last time point. The [%] remaining test compound after NADPH independent incubation is reflected by the parameter c (control) (metabolic stability). The quenched incubations are pelleted by centrifugation (10,000 g, 5 min). An aliquot of the supernatant is assayed by LC-MS/MS for the amount of parent compound.

The half-life (t½ INVITRO) is determined by the slope of the semilogarithmic plot of the concentration-time profile. The intrinsic clearance (CL_INTRINSIC) is calculated by considering the amount of protein in the incubation:

CL_INTRINSIC [μl/min/mg protein]=(ln 2/(half-life [min]*protein content [mg/ml]))*1,000.

The half-life (t½ INVITRO) values of selected compounds in the metabolic stability assay described above are listed in the following table

TABLE 69

Example	In vitro stability in human liver microsome incubations t½ [min]
2	>125
3	57
4	>130
5	92
6	>130
9	>120
10	>130
12	>130
14	>130
15	130
16	>130
19	>130
21	>130
22	>130
24	110
28	>130
29	>130
31	90
33	>130
35	>130
40	>130
41	>130
42	>130
43	>130
44	>130
47	84
49	>130
50	>130
52	>130
53	>130
54	>130
55	>130
57	95
58	>130
62	>130
67	89
71	>120
76	84
77	>130
78	130
82	>130
83	>130
86	>130
88	>130
89	>130
90	>130
91	>130
95	>130
96	82
97	>130
98	>130
99	>130
100	>130
102	>130

TABLE 69-continued

Example	In vitro stability in human liver microsome incubations t½ [min]
105	>130
106	>130
108	>130
109	>130
110	>130
111	>130
112	>130
114	>130
116	>130
117	>130
125	>130
132	>130
136	>130
139	>130
143	>130
147	>130
152	>130
153	110
154	>130
155	62
156	95
157	>130
158	>130
159	>130
162	>130
166	94
167	>130
169	>130
171	83
176	>130
178	>130
180	>120
181	>130
182	>130
183	>130
184	>130
185	>130
188	97
189	>130
190	>130
191	91
192	>130
193	>130
194	85
196	>130
199	88
200	>130
201	>130
204	>130
205	>130
218	>130
221	>130
222	>130
223	>130
230	>130
231	>130
233	>130
235	>130
236	>130
238	110
239	>130
240	110
241	84
242	>130
244	92
245	>130
247	>130
248	>130
249	>130
250	>130
252	130
253	>130
254	>130
255	>130
258	>130
259	>130

TABLE 69-continued

Example	In vitro stability in human liver microsome incubations t½ [min]
260	>130
261	>130
262	>120
263	>130
266	>130
267	>130
268	>130
269	>130
270	>130
271	130
272	>130
274	>125
276	130
277	>130
278	>130
281	>130
282	>130
283	>130
284	58
285	>130
288	>130
289	110
291	>130
292	94
293	>130
294	>130
295	>130
296	>130
298	105
300	>130
301	100
303	>130
305	91
306	>130
307	>130
308	>130
310	>130
313	>130
314	>130
315	92
319	>130
320	>130
321	>130
322	>130
323	>130
324	>130
325	>130
327	>130
328	>130
330	>130
331	>120
332	100
333	>130
335	>130
341	>130
342	>130
343	>130
344	110
345	>130
346	>130
347	>130
348	130
349	>130
358	>130
359	>130
WO09074829; Example 56	120

COMBINATIONS

The compounds of general formula I may be used on their own or combined with other active substances of formula I according to the invention. The compounds of general formula I may optionally also be combined with other pharmacologically active substances. These include, β2-adrenoceptor-agonists (short and long-acting), anti-cholinergics (short and long-acting), anti-inflammatory steroids (oral and topical corticosteroids), cromoglycate, methylxanthine, dissociated-glucocorticoidmimetics, PDE3 inhibitors, PDE4-inhibitors, PDE7-inhibitors, LTD4 antagonists, EGFR-inhibitors, Dopamine agonists, PAF antagonists, Lipoxin A4 derivatives, FPRL1 modulators, LTB4-receptor (BLT1, BLT2) antagonists, Histamine H1 receptor antagonists, Histamine H4 receptor antagonists, dual Histamine H1/H3-receptor antagonists, PI3-kinase inhibitors, inhibitors of non-receptor tyrosine kinases as for example LYN, LCK, SYK, ZAP-70, FYN, BTK or ITK, inhibitors of MAP kinases as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, inhibitors of the NF-κB signalling pathway as for example IKK2 kinase inhibitors, iNOS inhibitors, MRP4 inhibitors, leukotriene biosyntheses inhibitors as for example 5-Lipoxygenase (5-LO) inhibitors, cPLA2 inhibitors, Leukotriene A4 Hydrolase inhibitors or FLAP inhibitors, Non-steroidal anti-inflammatory agents (NSAIDs), CRTH2 antagonists, DP1-receptor modulators, Thromboxane receptor antagonists, CCR3 antagonists, CCR^4 antagonists, CCR1 antagonists, CCR5 antagonists, CCR6 antagonists, CCR7 antagonists, CCR8 antagonists, CCR9 antagonists, CCR30 antagonists, $CXCR^3$ antagonists, $CXCR^4$ antagonists, $CXCR^2$ antagonists, $CXCR^1$ antagonists, CXCR5 antagonists, CXCR6 antagonists, $CX3CR^3$ antagonists, Neurokinin (NK1, NK2) antagonists, Sphingosine 1-Phosphate receptor modulators, Sphingosine 1 phosphate lyase inhibitors, Adenosine receptor modulators as for example A2a-agonists, modulators of purinergic receptors as for example P2X7 inhibitors, Histone Deacetylase (HDAC) activators, Bradykinin (BK1, BK2) antagonists, TACE inhibitors, PPAR gamma modulators, Rho-kinase inhibitors, interleukin 1-beta converting enzyme (ICE) inhibitors, Toll-Like receptor (TLR) modulators, HMG-CoA reductase inhibitors, VLA-4 antagonists, ICAM-1 inhibitors, SHIP agonists, GABAa receptor antagonist, ENaC-inhibitors, Prostasin-inhibitors, Matriptase-inhibitors, Melanocortin receptor (MC1R, MC2R, MC3R, MC4R, MC5R) modulators, CGRP antagonists, Endothelin antagonists, TNFα antagonists, anti-TNF antibodies, anti-GM-CSF antibodies, anti-CD46 antibodies, anti-IL-1 antibodies, anti-IL-2 antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, anti-IL-13 antibodies, anti-IL-4/IL-13 antibodies, anti-TSLP antibodies, anti-OX40 antibodies, mucoregulators, immunotherapeutic agents, compounds against swelling of the airways, compounds against cough, VEGF inhibitors, NE-inhibitors, MMP9 inhibitors, MMP12 inhibitors, but also combinations of two or three active substances.

Preferred are betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists and SYK-inhibitors, NE-inhibitors, MMP9 inhibitors, MMP12 inhibitors, but also combinations of two or three active substances, i.e.:

- Betamimetics with corticosteroids, PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists,
- Anticholinergics with betamimetics, corticosteroids, PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists,
- Corticosteroids with PDE4-inhibitors, CRTH2-inhibitors or LTD4-antagonists
- PDE4-inhibitors with CRTH2-inhibitors or LTD4-antagonists
- CRTH2-inhibitors with LTD4-antagonists.

INDICATIONS

The compounds of the invention and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as inhibitors of dipeptidyl peptidase I activity, and thus may be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; alpha1-antitrypsin deficiency, bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, polyangiitis (Wegener Granulomatosis) and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;
3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;
4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;
7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoprolif-

erative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and *mycobacterium avium*, leprosy; other infectious diseases, such as fungal diseases, chlamydia, *Candida, aspergillus*, cryptococcal meningitis, *Pneumocystis carnii*, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

9. pain: Recent literature data from Cathepsin C-deficient mice point to a modulatory role of Cathepsin C in pain sensation. Accordingly, inhibitors of Cathepsin C may also be useful in the clinical setting of various form of chronic pain, e.g. inflammatory or neuropathic pain.

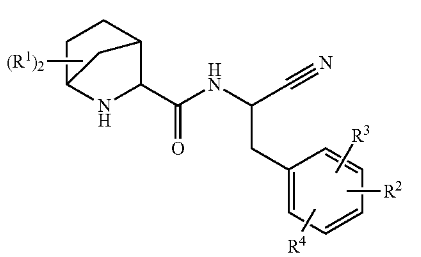
For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For Example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the active ingredient will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

We claim:

1. A compound of formula 1

1

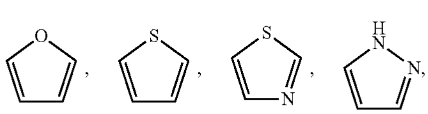


wherein

R^1 is independently selected from H, C_{1-6}-alkyl-, halogen, HO—, C_{1-6}-alkyl-O—, H_2N—, C_{1-6}-alkyl-HN—, $(C_{1-6}\text{-alkyl})_2N$— and C_{1-6}-alkyl-C(O)HN—;

or two R^1 are together C_{1-4}-alkylene;

R^2 is selected from



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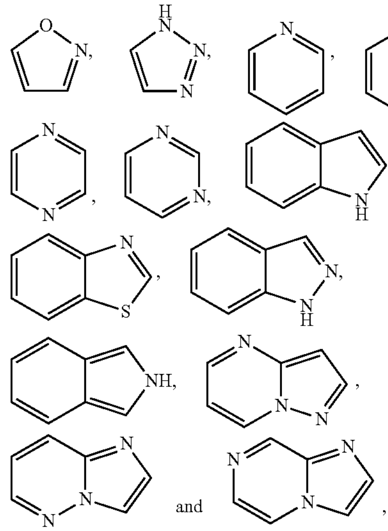


wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; and

$R^{2.1}$ is independently selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is independently selected from

aryl-; optionally substituted independently from each other with one, two or three $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-; containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-; containing one, two, three or four heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three or four $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl-; and

$R^{2.2}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-$S(O)_2$— and C_{1-4}-alkyl-C(O)—, $R^{2.1.1}$-A-;

$R^{2.3}$ and R^4 are together selected from —O—, —S—, —N($R^{2.3.1}$)—, —C(O)N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C(O)—, —$S(O)_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, —$S(O)_2$—, $R^{2.3}$, $R^{2.3}$, —C($R^{2.3.2}$)═C($R^{2.3.2}$)—, —C═N—, —N═C—, —C$(R^{2.3.2})_2$—O—, —O—C$(R^{2.3.2})_2$—, —C$(R^{2.3.2})_2$N($R^{2.3.1}$)—, and —N($R^{2.3.1}$)C$(R^{2.3.2})_2$— and —C_{1-4}-alkylene-;

$R^{2.3.1}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

$R^{2.3.2}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

$R^{2.4}$ and R^4 are together selected from —N($R^{2.4.1}$)—, —C(O)N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C(O)—, —$S(O)_2$N($R^{2.4.1}$)—, —N($R^{2.4.1}$)$S(O)_2$—, —C(O)—, —S(O)—, —$S(O)_2$—, —C($R^{2.4.2}$)═C($R^{2.4.2}$)—, —C═N—, —N═C—, —C$(R^{2.4.2})_2$N($R^{2.4.1}$)— and —N($R^{2.4.1}$)C$(R^{2.4.2})_2$—, —C_{1-4}-alkylene-; and

$R^{2.4.1}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

$R^{2.4.2}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

$R^{2.5}$ and R^4 are together selected from —C($R^{2.5.1}$)═, ═C($R^{2.5.1}$)—, —N═; and

$R^{2.5.1}$ is independently selected from H, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-; C_{3-8}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

R^3 is H or F;

R^4 is independently selected from F, Cl, phenyl-H_2C—O—, HO—, C_{1-6}-alkyl-, C_{1-6}-haloalkyl-, C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-O—, C_{1-6}-haloalkyl-O—, C_{1-6}-alkyl-HN—, $(C_{1-6}\text{-alkyl})_2$-HN—, C_{1-6}-alkyl-HN—C_{1-4}-alkylene- and $(C_{1-6}\text{-alkyl})_2$-HN—C_{1-4}-alkylene-;

A is a bond or independently selected from —O—, —S—, —N(R^5)—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5) $S(O)_2$—, —S(O)(═NR^5)—N(R^5)—, —N(R^5)(NR^5═) S(O)—, —S$(=NR^5)_2$—N(R^5)—, —N(R^5)$(NR^5=)_2$S—, —C(R^5)═C(R^5)—, C≡C—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, —$S(O)_2$—, —S(═NR^5)—, —S(O)(═NR^5)—, —S$(=NR^5)_2$—, —(R^5)(O)S═N—, —(R^5N═)(O)S—, and —N═(O)(R^5)S—;

R^5 is independently selected from H, C_{1-6}-alkyl- and NC—;

or a salt thereof.

2. The compound of formula 1, according to claim **1**, wherein R^1 is $R^{1.a}$ and $R^{1.a}$ is independently selected from H, C_{1-4}-alkyl-, F and HO—.

3. The compound of formula 1, according to claim **1**, wherein R^4 is $R^{4.a}$ and $R^{4.a}$ is F, Cl, phenyl-H_2C—O—, HO—, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O— and C_{1-4}-haloalkyl-O—.

4. The compound of formula 1, according to claim **1**, wherein R^4 is $R^{4.b}$ and $R^{4.b}$ is F.

5. The compound of formula 1, according to claim **1**, wherein A is A^a and A^a is a bond or independently selected from —O—, —C(O)N(R^5)—, —N(R^5)C(O)—, —$S(O)_2$N(R^5)—, —N(R^5)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —$S(O)_2$—, —(R^5)(O)S═N—, —(R^5N═)(O)S—, —N═(O)(R^5)S— and R^5 is $R^{5.a}$ and $R^{5.a}$ is independently selected from H, C_{1-4}-alkyl- and NC—.

6. The compound of formula 1, according to claim **1**, wherein R^2 is $R^{2.1}$ and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

7. The compound of formula 1, according to claim **1**, wherein R^2 is $R^{2.d}$ and $R^{2.d}$ is phenyl; optionally substituted with one, two or three residues independently selected from $R^{2.1}$ and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

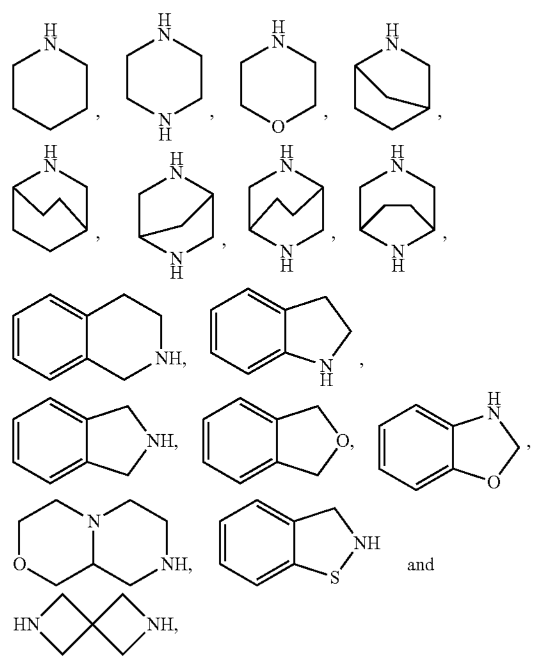
C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl.

8. The compound of formula 1, according to claim **1**, wherein R^2 is $R^{2.j}$ and $R^{2.j}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-; optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-; containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-; containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three or four $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl-; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-$S(O)_2$—, C_{1-4}-alkyl-C(O)—, and $R^{2.1.1}$-A-.

9. The compound of formula 1, according to claim **1**, wherein R^2 is $R^{2.m}$ and $R^{2.m}$ is together with R^4 and two adjacent carbon atoms of the phenyl ring a 5- or 6-membered aryl or heteroaryl, containing one, two or three heteroatoms independently selected from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.2}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-; optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-; containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

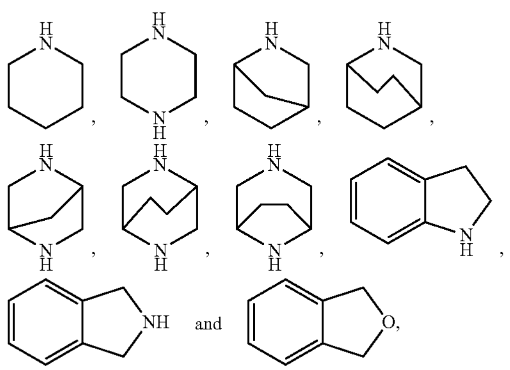
C_{5-10}-heterocyclyl-; containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three or four $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl-; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-$S(O)_2$—, C_{1-4}-alkyl-C(O)—, and $R^{2.1.1}$-A-.

10. The compound of formula 1, according to claim **1**, wherein R^2 is $R^{2.n}$ and $R^{2.n}$ is selected from aryl-, pyrazole, thiophene, furane; wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; or $R^{2.n}$ is selected from



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$, wherein possibly available nitrogen atoms of the ring are optionally and independently from each other substituted with $R^{2.2}$; wherein a carbon atom of the ring is optionally substituted with one $R^{2.3}$ or one $R^{2.5}$; a nitrogen atom of the ring is optionally substituted with one $R^{2.4}$; and

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-; optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-; containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

C_{5-10}-heterocyclyl-; containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three or four $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl-; and

$R^{2.2}$ is $R^{2.2.a}$ and $R^{2.2.a}$ is independently selected from H-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-$S(O)_2$—, C_{1-4}-alkyl-C(O)—, and $R^{2.1.1}$-A-; and

$R^{2.3}$ is together with R^4 a group $R^{2.3.a}$ and $R^{2.3.a}$ is selected from —O—, —S—, —N($R^{2.3.1}$)—, —C(O)N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C(O)—, —$S(O)_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)$S(O)_2$—, —C(O)O—, —OC(O)—, —C(O)—, —S(O)—, —$S(O)_2$—, —C($R^{2.3.2}$)═C($R^{2.3.2}$)—, —C═N—, —N═C—, —C$(R^{2.3.2})_2$—O—, —O—C$(R^{2.3.2})_2$—, —C$(R^{2.3.2})_2$N($R^{2.3.1}$)—, —N($R^{2.3.1}$)C$(R^{2.3.2})_2$— and —C_{1-4}-alkylene-; and

$R^{2.3.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-;

$R^{2.3.2}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, (C_{1-4}-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, (C_{1-4}-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}\text{-alkyl})_2$N—C_{1-4}-alkylene-; and

$R^{2.4}$ is together with R^4 a group $R^{2.4.a}$ and $R^{2.4.a}$ is selected from —N($R^{2.4.1}$)—, —C(O)N($R^{2.4.1}$)—, —N($R^{2.4.1}$)C(O)—, —$S(O)_2$N($R^{2.4.1}$)—, —N($R^{2.4.1}$)$S(O)_2$—, —C(O)—, —S(O)—, —$S(O)_2$—, —C($R^{2.4.2}$)═C($R^{2.4.2}$)—, —C═N—, —N═C—, —C$(R^{2.4.2})_2$N($R^{2.4.1}$)—, and —N($R^{2.4.1}$)C$(R^{2.4.2})_2$—, —C_{1-4}-alkylene-; and

$R^{2.4.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, $(C_{1-4}$-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, $(C_{1-4}$-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}$-alkyl$)_2$N—C_{1-4}-alkylene-;

$R^{2.4.2}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, $(C_{1-4}$-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, $(C_{1-4}$-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}$-alkyl$)_2$N—C_{1-4}-alkylene-; and

$R^{2.5}$ is together with R^4 a group $R^{2.5.a}$ and $R^{2.5.a}$ is selected from —C($R^{2.5.1}$)═, ═C($R^{2.5.1}$), and —N═; and

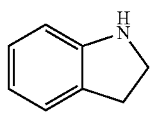
$R^{2.5.1}$ is independently selected from H, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, HO—C_{1-4}-alkylene-, $(C_{1-4}$-alkyl)-O—C_{1-4}-alkylene-, H_2N—C_{1-4}-alkylene-, $(C_{1-4}$-alkyl)HN—C_{1-4}-alkylene- and $(C_{1-4}$-alkyl$)_2$N—C_{1-4}-alkylene-.

11. The compound of formula 1 according to claim **1**, wherein

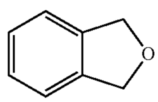
R^1 is $R^{1.b}$ and $R^{1.b}$ is H;

R^2 is $R^{2.q}$ and $R^{2.q}$ is selected from among the substituents (a1) to (q1)

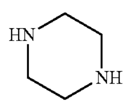
(a1)



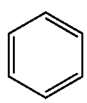
(b1)



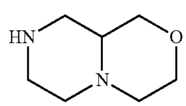
(c1)



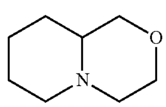
(d1)



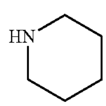
(e1)



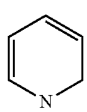
(f1)



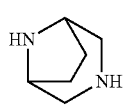
(g1)



(h1)

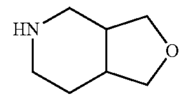


(i1)

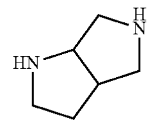


-continued

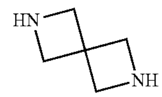
(j1)



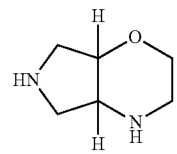
(k1)



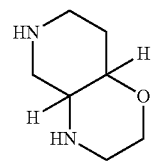
(l1)



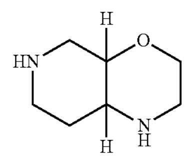
(m1)



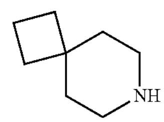
(n1)



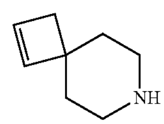
(o1)



(p1)



(q1)



wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two, three or four $R^{2.1}$; wherein possibly available nitrogen atoms of the ring are optionally and independently from each other are substituted with $R^{2.2}$;

or a salt thereof.

12. The compound of formula 1 according to claim **1**, wherein R^2 is $R^{2.s}$ and $R^{2.s}$ is Phenyl-$R^{2.3}$,

wherein the phenyl ring is optionally substituted with one or two residues $R^{2.1}$, wherein

$R^{2.1}$ is $R^{2.1.a}$ and $R^{2.1.a}$ is selected from H, halogen, NC—, O═, HO—, H-A-, H-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-, C_{1-4}-alkyl-A-, C_{3-6}-cycloalkyl-A-, C_{1-4}-haloalkyl-A-, $R^{2.1.1}$—C_{1-4}-alkylene-A-, C_{1-4}-alkyl-A-C_{1-4}-alkylene-, C_{3-6}-cycloalkyl-A-C_{1-4}-alkylene-, C_{1-4}-haloalkyl-A-C_{1-4}-alkylene-, $R^{2.1.1}$—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, $R^{2.1.1}$-A-C_{1-4}-alkylene-, HO—C_{1-4}-alkylene-A-, HO—C_{1-4}-alkylene-A-C_{1-4}-alkylene-, C_{1-4}-alkyl-O—C_{1-4}-alkylene-A- and C_{1-4}-alkyl-O—C_{1-4}-alkylene-A-C_{1-4}-alkylene-; and

$R^{2.1.1}$ is $R^{2.1.1.a}$ and $R^{2.1.1.a}$ is selected from

aryl-, optionally substituted independently from each other with one, two or three residues independently selected from $R^{2.1.1.1}$;

C_{5-10}-heteroaryl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$;

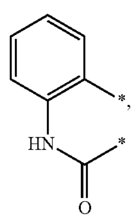
C_{5-10}-heterocyclyl-, containing one, two, three or four heteroatoms selected independently from S, S(O), $S(O)_2$, O and N, and the ring is fully or partially saturated, wherein carbon atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.1}$; wherein nitrogen atoms of the ring are optionally and independently from each other substituted with one, two or three $R^{2.1.1.2}$; and

$R^{2.1.1.1}$ is independently selected from halogen, HO—, O═, C_{1-4}-alkyl-, C_{1-4}-alkyl-O—, C_{1-4}-haloalkyl-, C_{1-4}-haloalkyl-O— and C_{3-6}-cycloalkyl-; and

$R^{2.1.1.2}$ is independently selected from O═, C_{1-4}-alkyl-, C_{1-4}-haloalkyl-; C_{3-6}-cycloalkyl-, C_{1-4}-alkyl-O—C_{1-4}-alkyl-, H(O)C—, C_{1-4}-alkyl-(O)C—, tetrahydrofuranylmethyl- and tetrahydropyranylmethyl;

and $R^{2.s}$ and R^4 together denote a group (r1),

(r1)



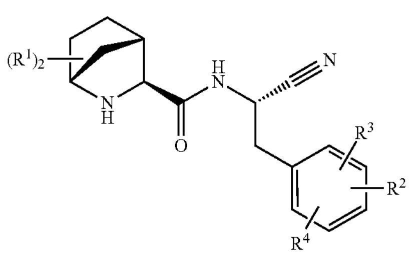
wherein the N-atom is optionally substituted with —$R^{2.2}$, wherein

$R^{2.2}$ is independently selected from H-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-, C_{1-6}-alkyl-A-C_{1-6}-alkylene-, C_{3-8}-cycloalkyl-A-C_{1-6}-alkylene-, C_{1-6}-haloalkyl-A-C_{1-6}-alkylene-, $R^{2.1.1}$-A-C_{1-6}-alkylene-, C_{1-6}-alkyl-$S(O)_2$—, C_{1-6}-alkyl-C(O)— and $R^{2.1.1}$-A-;

or a salt thereof.

13. A compound of formula 1'

1'



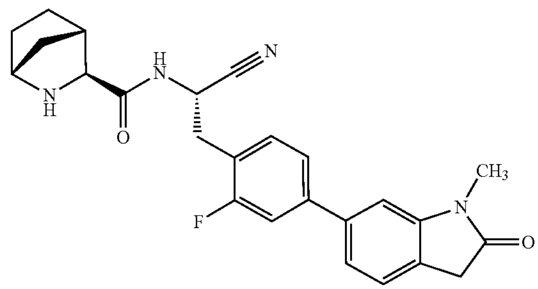
wherein R^1, R^2, R^3 and R^4 have the meaning of claim **1**.

14. A pharmaceutical composition comprising a compound of formula 1 according to claim **1** or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition according to claim **14** further comprising a pharmaceutically active compound selected from the group consisting of betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, CRTH2 inhibitors, 5-LO-inhibitors, Histamine receptor antagonists, CCR9 antagonists and SYK-inhibitors, NE-inhibitors, MMP9 inhibitors and MMP12 inhibitors, or combinations of two or three the pharmaceutically active compound.

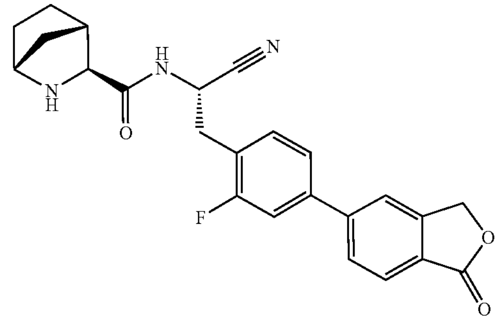
16. A method of treating asthma and allergic diseases, gastrointestinal inflammatory diseases, eosinophilic diseases, chronic obstructive pulmonary disease, infection by pathogenic microbes, rheumatoid arthritis or atherosclerosis comprising administering to a patient a therapeutically effective amount of a compound according to claim **1**.

17. A compound selected from



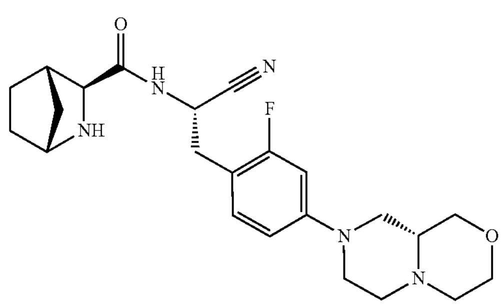
or a pharmaceutically acceptable salt thereof.

18. A compound selected from



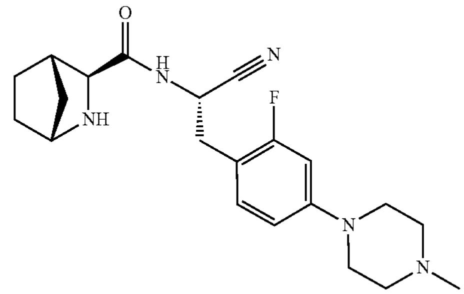
or a pharmaceutically acceptable salt thereof.

19. A compound selected from



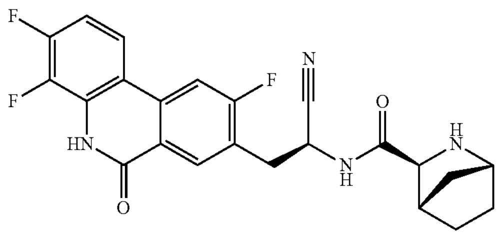
or a pharmaceutically acceptable salt thereof.

20. A compound selected from



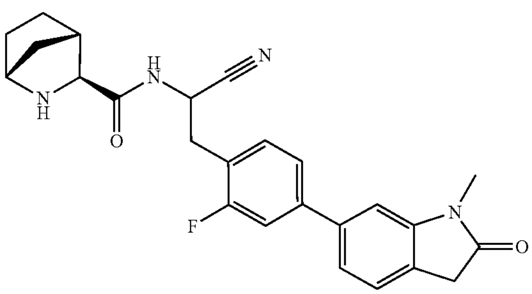
or a pharmaceutically acceptable salt thereof.

21. A compound selected from



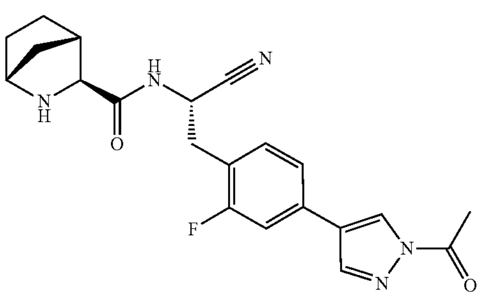
or a pharmaceutically acceptable salt thereof.

22. A compound selected from



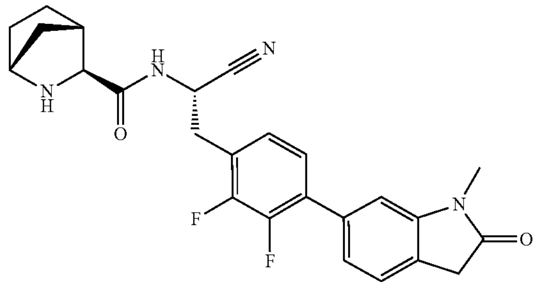
or a pharmaceutically acceptable salt thereof.

23. A compound selected from



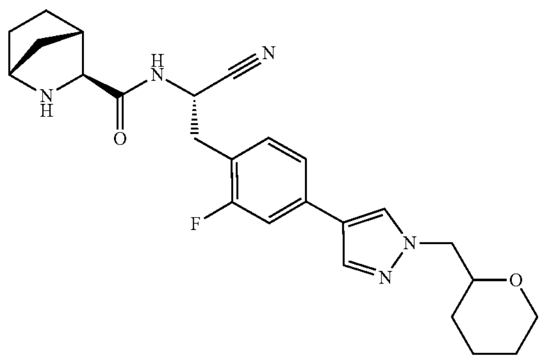
or a pharmaceutically acceptable salt thereof.

24. A compound selected from



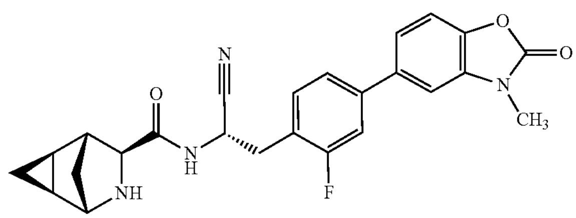
or a pharmaceutically acceptable salt thereof.

25. A compound selected from



or a pharmaceutically acceptable salt thereof.

26. A compound selected from



or a pharmaceutically acceptable salt thereof.

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